Volume 12, Number 6

DECEMBER 1952

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References:
1. Kuzell, W. C., and Schaffarzick, R. W.: Paper read before the California Medical Association, Los Angeles, April 29, 1952.
2. Smith, C. H., and Kunz, H. G.: J. M. Soc. New Jersey *49*:306, 1952.
3. Currie, J. P.: Lancet *2*:15 (July 5) 1952.
4. Hart, F. D., and Johnson, A. M.: Lancet *2*:43 (June 5) 1952.
5. Kuzell, W. C.; Schaffarzick, R. W.; Brown, B., and Mankle, E. A.: J.A.M.A. *149*:729 (June 21) 1952.
6. Holbrook, W. P.; Stephens, C. A. L., Jr.; Yeoman, E. E.; Hill, D. F., and Goodin, W. L.: Personal communication — July 18, 1952.

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• PHYSICAL ALLERGY TO COLD

Question: A 40 year old married woman, a laundress, develops mild to moderately severe urticaria from the fingertips to the elbows and from the toes to the knees whenever she is exposed early in the morning to cold water when she washes clothes. The condition has been recurring now and then for over a year. She denies any history of allergy in the family. Food does not seem to influence or provoke any similar skin reaction. Warm baths apparently do not excite any skin rash. Antihistaminics have been tried with temporary relief. None of the known sympathomimetics tried did her much good.

What could be the nature of the allergens causing the reaction, possibly released after cold water as the excitant factor?

I would appreciate an opinion and/or suggestions with regard to latest methods of treatment. What possible allergen might be used for desensitization, if any?

Could you supply some references to literature on the subject?

M.D.—Philippines

ANSWER: The patient described is suffering from a form of physical allergy due to cold. The allergen is cold.

It is sometimes possible to hyposensitize these individuals by systematic exposure to gradually lowered temperatures by immersion in warm water, gradually lowering the temperature of the water to the point where sensitization begins. This method is very time-consuming and is not always successful.

A better method is the subcutaneous injection of histamine diphosphate, starting with 0.05 cc. of the 0.275 dilution, increasing the dose 0.05 of a cubic centimeter twice daily until 0.5 cc. is reached. This should be continued over a long period of time. After the third week it may be given twice weekly.

References—(1) Abramson: Treatment of Asthma. Williams and Wilkins, chapter 10, page 201, and (2) Urbach and Gottlieb: Allergy. Grune and Stratton, chapter 17, pages 409 to 415.

HARRY L. ROGERS

• AURICULAR FLUTTER IN MITRAL STENOSIS

Question: What is the proper treatment of auricular flutter occurring suddenly in a case of mitral stenosis?

M.D.—Illinois

ANSWER: The accepted treatment of auricular flutter occurring in a case of mitral stenosis is full digitalization. If this does not break up the flutter into a rhythm of auricular fibrillation and then result in a return to normal sinus rhythm, quinidine, 3 gr. four times a day, should be used. If this, combined with the digitalis, does not break up the flutter, the quinidine dosage can be increased to 6 gr. and even to as much as 9 gr. four times a day.

WILLIAM D. STROUD

• BLACKOUTS AND MENTAL RETARDATION

Question: I have a female patient 3 years old who has developed normally physically but is mentally retarded. At 6 months of age it was noted that she was not sitting up and would not notice anything. A definite nystagmus was noted in the right eye. All reflexes are normal. There have been no convulsions.

During the past year the child has made much improvement. She crawls and stands up, walks when her hand is held, notices everything, and plays. She does not talk but has all the sounds.

(Continued on page A-28)

WHEN DIETARY SUPPLEMENTATION IS NEEDED...

what more could a supplement provide?

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CHLORINE	900 mg.	BIOTIN	0.03 mg.
COBALT	0.006 mg.	CHOLINE	200 mg.
*COPPER	0.7 mg.	FOLIC ACID	0.05 mg.
FLUORINE	3.0 mg.	*NIACIN	6.7 mg.
*IODINE	0.7 mg.	PANTOTHENIC ACID	3.0 mg.
*IRON	12 mg.	PYRIDOXINE	0.6 mg.
MAGNESIUM	120 mg.	*RIBOFLAVIN	2.0 mg.
MANGANESE	0.4 mg.	*THIAMINE	1.2 mg.
*PHOSPHORUS	940 mg.	*VITAMIN A	3200 I.U.
POTASSIUM	1300 mg.	VITAMIN B_{12}	0.005 mg.
SODIUM	560 mg.	*VITAMIN D	420 I.U
ZINC	2.6 mg.		

*PROTEIN (biologically complete)	32 Gm.
*CARBOHYDRATE	65 m.
*FAT	30 Gm.

*Nutrients for which daily dietary allowances are recommended by the National Research Council.

The right eye nystagmus is now practically absent. She has a definite mind of her own. She is not trained in toilet habits. She eats well.

She has occasional blackouts lasting three to five seconds. If she is holding anything she does not drop it.

From the above summary, is a definite program possible? What would be the treatment for the blackouts?

Examination by a neurologist showed no evidence of brain tumor. Does the possibility of trauma enter here? PITUITRIN® and forceps were used at birth.

M.D.—Nova Scotia

ANSWER: The history as given indicates the probable presence of petit mal attacks. Complete study of the child, including an electroencephalogram, would be of value. It is possible that the attacks could be controlled with TRIDIONE® in doses from 0.3 to 0.9 gm. It is unlikely that trauma is a factor. The presence of retarded mental development in all probability means abnormality in the development of the central nervous system with the secondary effect of "blackouts."

• IMMUNIZATIONS FOR WORLD TRAVEL

Question: I am inquiring regarding immunization to be given to a family of five (two adults and three children) who are taking a world tour on a freighter. They are planning to visit many different parts of the world. They have been told that they will need (1) yellow fever, (2) typhoid, (3) cholera, (4) smallpox, (5) plague, (6) tetanus and (7) diphtheria immunizations.

The yellow fever shot is to be given first and, as I understand it, to be given through the Health Agency in San Francisco.

I would appreciate knowing the order in which these vaccinations and immunizations should be given; also, which preparations are presently recommended, especially in regard to cholera and plague.

M.D.—California

ANSWER: The types of immunizations required of people taking a world tour depend on the countries at which they will stop. When this information is available, one can obtain from the State Health Department information about which immunizations are required by the World Health Organization.

The order in which the immunizations are given is unimportant. The United States Public Health Service recommends that the yellow fever vaccine and the smallpox vaccination be given at least five days apart. Cholera and plague vaccine can be obtained from any of the pharmaceutical houses.

RUTH E. BOYNTON

• EFFECT OF DRUGS ON DIABETIC PATIENTS

Question: What drugs or groups of drugs are contraindicated in a patient with diabetes mellitus, and what is the rationale of the contraindications? For example, why is T.A.B. inoculation contraindicated?

M.D.—British Columbia

ANSWER: There are few drugs which are absolutely contraindicated for patients who have diabetes mellitus. Although certain drugs have the property of causing a temporary exacerbation of diabetes, they are not contraindicated if markedly beneficial effects can be expected from their use. For example, a variety of vaccines may give rise to a systemic reaction which results in temporary intensification of the diabetes, but this effect is temporary and, as a rule, the diabetes soon returns to its previous state. Such exacerbations can be treated successfully by diet and insulin. Likewise, cortisone and corticotropin are likely to intensify pre-existing diabetes, but they may be used for diabetic patients if significant benefit to a coexisting condition can be expected. Morphine and other drugs which have a respiratory depressant action are contraindicated in the presence of diabetic acidosis or coma because they may greatly accentuate the acidosis.

A variety of other drugs may give rise to false positive results of tests for glucose or diacetic acid in the urine, and this fact must be appreciated if they are used. These include aspirin, sulfonamides, morphine, ascorbic acid and thiamine. However, if their possible effect on urine tests is borne in mind, their use is not contraindicated.

The use of ether as an anesthetic agent may be undesirable in diabetic patients because it causes hepatic glycogenolysis. Its use, however, is not contraindicated if it offers other advantages and the physician appreciates its possible effects on the diabetes.

Prospects for Earlier Diagnosis of Carcinoma of the Stomach

LEROY R. SANTE*

St. Louis University School of Medicine, St. Louis

Cancer of the stomach is one of the most frequent causes of death in the United States today. Its onset is insidious, and it remains undiscovered until by its growth it interferes with function. Surgery offers only scant chance of cure. One bright spot looms on the horizon: the development of a device for intensification of the x-ray fluoroscopic image, by which diagnosis may be possible at an earlier date.

L. R. SANTE

We are all acutely conscious of the magnitude of the cancer problem today. Cancer is one of the topmost causes of death at the present time. As has been pointed out, cancer of the stomach alone is responsible for three times as many deaths as automobile accidents, and twice as many as active warfare, in our country. Such a destructive force is obviously a great economic loss to the nation.

The treatment of cancer today looks to the complete removal of the local growth. Early diagnosis, therefore, is of prime importance if the area of involvement is to be completely eradicated. Once the disease has spread beyond the confines of its original growth, its complete removal becomes almost impossible. The question, therefore, "Is there a method for early diagnosis of carcinoma of the stomach?" becomes predicated upon early recognition of the disease when the original lesion is small and before it has spread from its original site. The purpose of this paper, then, will be to evaluate our present methods of diagnosis and treatment, especially that of roentgenologic examination, to analyze their advantages and shortcomings and to explore any prospects of advancement for the future.

There is hardly any other field in cancer therapy where the results are so poor. Radiation therapy is of no value whatever, and surgical resection offers little hope. Less than 1 per cent five year survivals, the prevailing salvage rate for many years, always stands out as an indication of the shortcomings of this procedure as a curative measure. These were patients in whom, after exploration, there seemed to be reasonable hope for success; only the most favorable cases were finally resected.

In recent years the percentage of five year survivals after gastric resection for carcinoma has been increased somewhat; claims as high as 5 per cent have been recorded in some instances. Where the statistics in general are so low, claims of high survivals made by a few men sound fantastic and lead one to suspect that an overenthusiastic pathologist has been erroneously led to the diagnosis of malignant disease on insufficient microscopic evidence. We must be very wary lest statistics lead us astray.

*Professor of Radiology, St. Louis University School of Medicine; President, St. Louis Medical Society, St. Louis, Missouri.

Presented at the thirty-sixth (St. Louis) annual Assembly of the Interstate Postgraduate Medical Association.

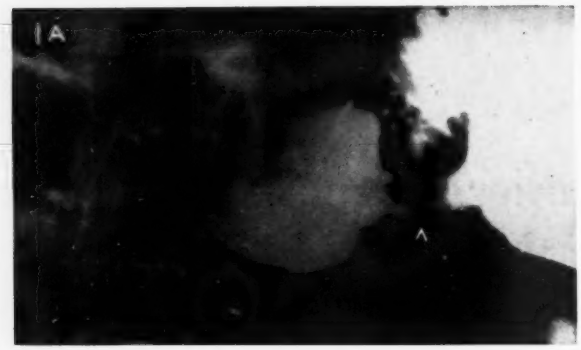


FIGURE 1a. Small polyp springing from the prepyloric mucosa, producing a rounded filling defect. b. Small niche due to prepyloric ulcer. Ulcers in this location frequently develop within a malignant base.

In former days it was the fashion to resect all ulcers of the stomach and then to institute microscopic search by serial sections of the specimen for evidence of malignancy. This was done on the supposition that chronic ulcers were likely to undergo malignant degeneration in this location, the same as elsewhere. Such procedure frequently resulted in a false diagnosis of malignant changes in the margins of ulcers on the appearance of a few cells. One can readily understand how, in a large clinic where a punch card system was in use to record statistics in assembling the follow-up results five years later, such a diagnosis would appear just as valid as if there had been an actual carcinomatous mass present; furthermore, the heading "Surgical Resection" might not carry any distinction between local removal of an ulcer and resection of two-thirds of the stomach together with regional lymphatic glands. Under such conditions the five year survival statistics of carcinoma of the stomach after operative resection might climb to any height.

Recent Statistics

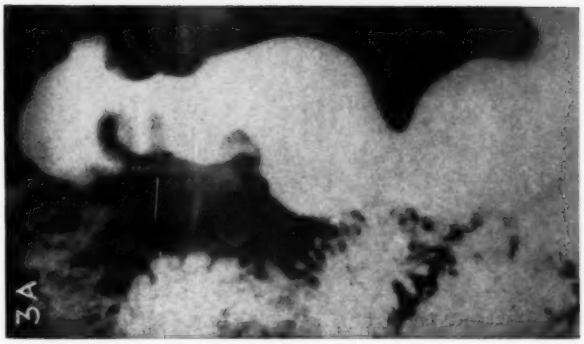
Analysis of recent statistics has shown a somewhat brighter picture. Although operative procedures for gastric carcinoma occurring in the fundus or pas media, or diffusely involving the entire stomach, do not result in any five year survivals, it has been found that resection of carcinoma of the pyloric portion of the stomach in suitable cases may result in 18.9 per cent five year survivals. Although still woefully small—since 48 per cent of all carcinoma occurs within the pyloric area—this would seem to indicate definite progress in the attack on this prevalent disease. Furthermore, these results would serve to point out precise operative indications.

The cause of this failure to accomplish more worthwhile results in the operative resection of gastric cancer has been generally ascribed to the failure to detect the disease at an early stage.

FIGURE 2a. Small polypoid growths may easily go undetected when overshadowed by barium mixture. b. Small polypoid growth demonstrated in same patient, with smaller quantity of barium in stomach.

Indeed, it is undoubtedly true that if detected at an earlier stage, more satisfactory results might be expected. The difficulty arises from the fact that cancer of the stomach, in the early stages, is so insidious in its origin; not until it interferes with function by reason of its size or location or by its ulceration does it produce sufficient symptoms to direct attention to its presence. By this time the growth usually has attained such size that effective surgery is not possible.

The matter of earlier detection of carcinomatous lesions of the stomach by radioscopic methods would involve, therefore, the examination of patients without symptoms and apparently in good health. Every radiologist has seen a few early carcinomatous lesions, discovered quite by accident in patients examined for some other type of lesion (Figure 1)—small lesions a centimeter or so in size on the mucosal surface, and perhaps an occasional polyp (Figure 2). Such examinations are beset with many difficulties (Figures 3 and 4). Carcinomatous lesions of the fundus of the stomach are perhaps among those



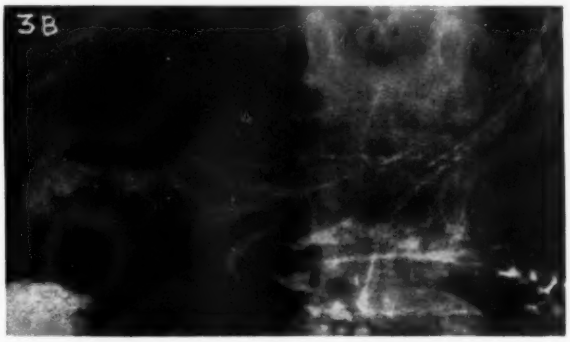
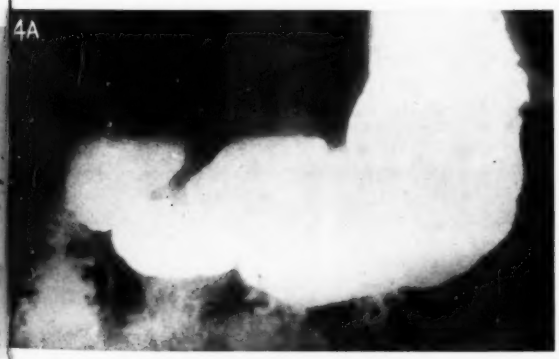


FIGURE 3a. Irregular appearance of stomach in pyloric region might easily be suspected as carcinoma. b. Mucosal study shows plainly the rounded niche or a benign ulcer.



most difficult to detect; in this location, cure by operative procedure or any other method is nil anyway, so that even if the diagnosis is missed, little is lost in the ultimate salvage from the disease (Figure 5). In linitis plastica also, diffuse infiltration of the stomach wall gives a picture which, in the early stages, may often be difficult to recognize. Giant rugae of the benign type may be so pronounced and the mucosa may be so redundant that they may closely resemble carcinoma; when benign in character they usually involve the entire stomach; when localized to a small area of the stomach they must be viewed with suspicion since they may represent malignant infiltration, often of the lymphogranulomatous type, lymphosarcoma or Hodgkin's disease.

Ulceration of a carcinomatous growth, however, may occur very early, even when the

FIGURE 4a. Pyloric end of stomach with complete filling. b. Mucosal relief showing giant rugae. These may closely resemble malignant growth.

FIGURE 5a. Carcinomatous growth of the fundus causing deflection of the barium stream as it enters the stomach. Tumors in this region may easily escape detection. b. Linitis plastica, or generalized infiltration of the entire gastric wall, may, in its early stages, be readily overlooked.

lesion is quite small, giving rise to pain. This is at least one phase in which roentgenologic investigation may be of value in the early diagnosis of carcinomatous lesions. Indeed, such ulcerating malignant lesions are most prone to occur in the prepyloric area, and in this region the operative results of resection are the most favorable.

That some ulcerations of the stomach are malignant, there can be no doubt, but that these are primarily malignant lesions which have subsequently undergone ulceration, rather than primary benign ulcers which have undergone malignant degeneration, there is every indication to believe.

Benign and Malignant Characteristics

Kirklin has outlined the conditions influencing the benign or malignant characteristics of gastric ulcers (Figure 6) as follows:

"An ulcer may be considered as probably benign when (1) the duration of the symptom is 10 years or more; (2) the patient's age is 30 years or less; (3) there is a free hydrochloric acid determination of 40 or more; (4) at roentgenologic examination the ulceration goes through the wall; (5) the lesion is found at roentgenographic examination on the lesser curvature; (6) the crater of the ulcer measures 2 cm. or less; (7) the stomach is of the 'B' type; (8) the biologic test shows reduction of size of the crater under medical treatment.

"An ulcer may be considered as probably malignant when (1) the symptoms are of recent onset; (2) in an elderly individual; (3) there is

FIGURE 6a. Benign ulcer of stomach showing pouch-like niche on lesser curvature. b. Pressure over niche in barium-filled stomach shows clearcut margins of ulcer crater with rugae radiating in toward the ulcer.

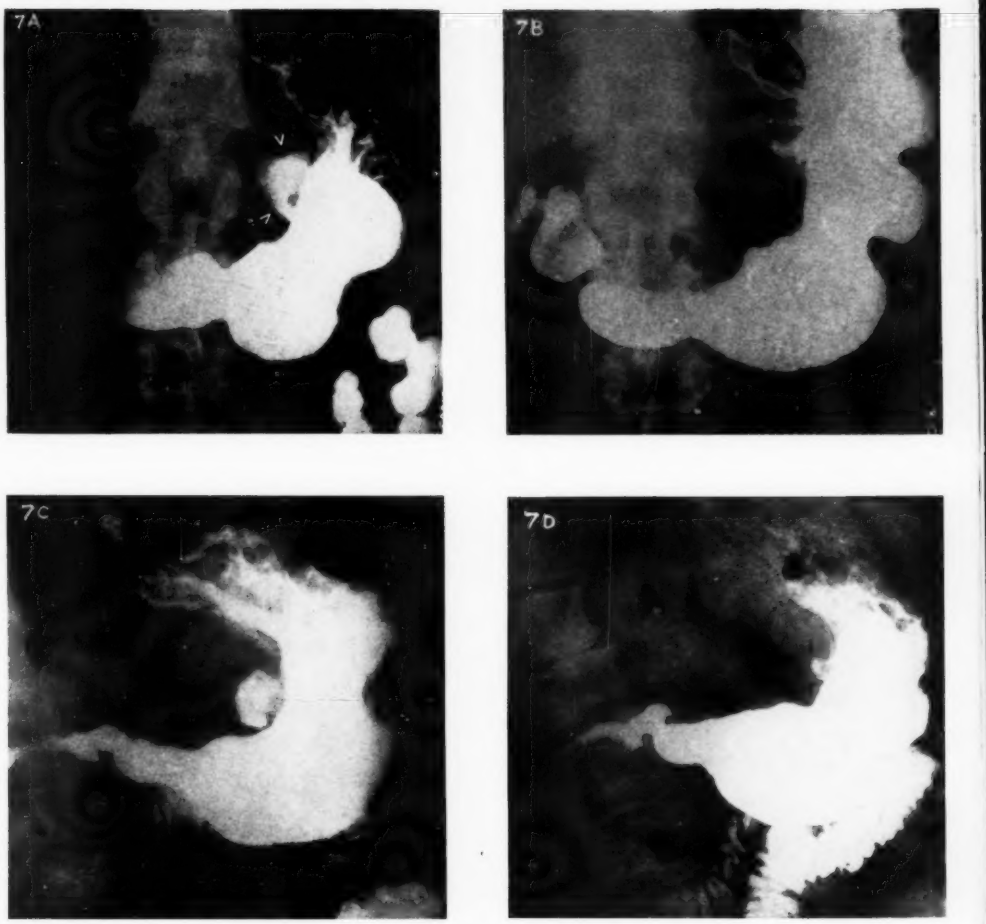


FIGURE 7a. Irregular-appearing niche on lesser curvature. b. Marked healing after 20 days of bed rest; such improvement indicates benign character of the ulceration. c. Another patient showing large, irregular ulcer on lesser curvature; because of its size it looks malignant. d. Almost complete healing after eight weeks of bed rest, indicating its benign character.

an achylia; (4) at roentgen examination the ulcer is irregular in outline, especially if it shows a meniscus sign; (5) the lesion is located in the prepyloric region, posterior wall, or greater curvature; (6) the crater is 2.5 cm. or more in size; (7) the biologic test shows no healing of the ulcer under proper medical regime."

It would seem, then, that in an individual showing a niche 2 cm. or less in size occurring on the lesser curvature, going through the stomach wall and producing a "B" shaped deformity of the stomach, the ulceration is probably benign if it occurs in a young individual who has had symptoms of indigestion for a considerably prolonged period, especially if the gastric analysis shows a high level of hydrochloric acid.

On the other hand, an irregular ulceration larger than 2.5 cm. in diameter occurring elsewhere than on the lesser curvature, especially in the pyloric region, posterior wall or greater curvature, is very likely to be malignant if it occurs in an elderly individual who has not suffered from chronic indigestion, and particularly in the absence of hydrochloric acid (Figure 7).

It is the consensus among roentgenologists that primary gastric ulcers are benign and always remain benign, that they do not undergo malignant degeneration. A large majority occur on the lesser curvature and are represented roentgenographically by a niche. Many instances have been observed in which gastric ulcers have per-

FIGURE 8a. Meniscus sign showing infiltration of base of ulcer. This is indication of the malignant character of the ulceration. b. With pressure, a true meniscus sign must show the ulcer to be entirely intrinsic; it represents ulceration which has developed within a carcinomatous growth.

FIGURE 9a. Benign ulcer of the stomach on the lesser curvature. b. Complete permanent healing after 20 days of strict bed rest.

sisted for as long as 8 to 10 years without showing material change. Such benign ulcers have a punched-out appearance; the adjacent rugae are well preserved to the very margin of the ulceration, and the rugae seem to be drawn inward due to a puckering action.

Malignant ulcerations arise primarily as tumors which later undergo ulceration; the ulceration in such cases is usually eccentric and asymmetric. The edges of such malignant ulcers are thickened and indurated, and the adjacent rugae are obliterated by the infiltrating carcinoma. Such an infiltrative border may give rise to a meniscus sign (Figure 8). This sign was originally described by Carman as an invariable indication of malignant character of an ulceration. Kirklin has pointed out that to be a true meniscus sign the lesion must be entirely intraluminal. The sign depends on the indurated infiltrating border of the ulcerated area.

The mere size of the crater, likewise, may not be an infallible index of malignancy. We have encountered chronic ulcers more than 3 or 4 cm. in size which, on microscopic examination, did not have any pathologic manifestation of malignancy.

The most reliable test for assaying the malignant or benign character of an ulcer is to observe its behavior for a brief period of time—two to three weeks (Figure 9). A carcinomatous ulceration will not show any indication of regression but may even get larger in size with conservative treatment, whereas a benign gastric ulcer will show prompt healing under such a medical regimen. It would seem wise, therefore, in case of doubt, to subject the patient to

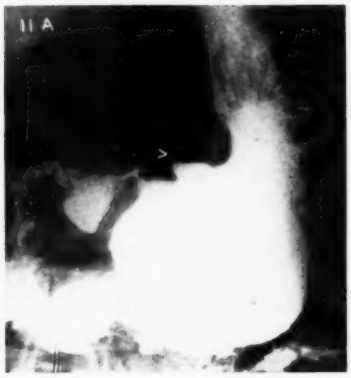


FIGURE 10a and b. Benign ulcer of the stomach on lesser curvature. c and d. Complete, permanent healing after bed rest.

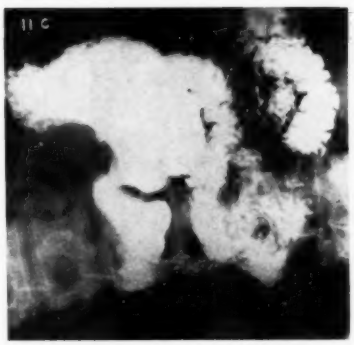
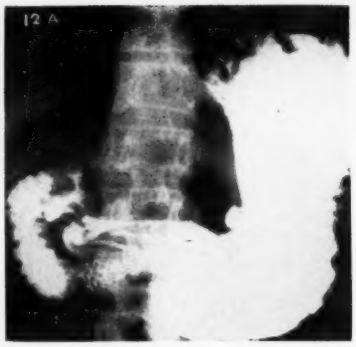


FIGURE 11a. Perforating ulcer of stomach with niche and gas bubble. b. Showing healing after four weeks. c. Further healing after six weeks. d. Completely healed after eight weeks.

such a test before radical surgery is undertaken.

If a patient with benign gastric ulcer, such as that described, is subjected to *absolute bed rest without alkalinization, special medication or diet,* and is merely given unrestricted amounts of nourishing food, he will, in a great majority of instances, be relieved of pain within a few days and his ulcer crater will show spontaneous healing (Figure 10). Although this observation has been known to radiologists for many years, it still seems to lack general acceptance. Radiologists have been struck with the fact that gastric ulcers occur almost exclusively on the lesser curvatures of stomachs of the hypotonic type—those which, in the upright position, sag down into the lower abdomen. Hypertonic or "steer horn" stomachs are almost universally free from gastric (not duodenal) ulcer. Assuming that this may be on the basis of ischemia of the lesser curvature due to the dragging downward of the hypotonic stomach, it is natural to assume that absolute bed rest, causing relief of this ischemia,



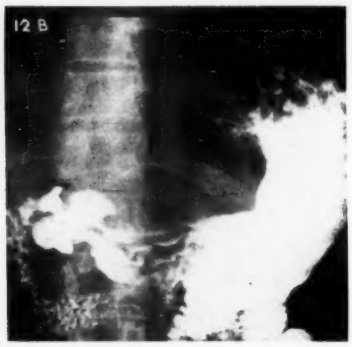


FIGURE 12a. Gastric and duodenal ulcer occurring in same patient. This is not extremely uncommon. b. Gastric ulcer healed after bed rest. Duodenal ulcer persists. Whatever the case, duodenal ulcer does not respond like gastric ulcer to bed rest.

FIGURE 13. Benign ulcer of the lesser curvature of the stomach, with associated carcinomatous lesion of the pylorus, a most unusual combination.

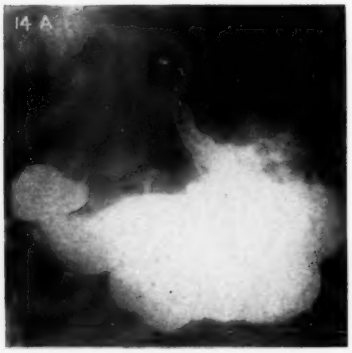


FIGURE 14a. Large ulcer crater in pyloric region resembling duodenal bulb. b. Same patient in prone position, showing complete filling of crater and indurated margin. In spite of these indications of malignancy, the ulcer proved to be benign.

FIGURE 15. Large ulcer crater in pyloric region. On section, a large roundworm was found in base of ulcer.

would have a favorable effect on such a condition. Ulcers 1 cm. in diameter usually show reduction in size in two to three weeks and may be completely healed in four weeks; those larger than 1 cm. in diameter may take longer, even up to six to eight weeks. Even when such ulcers have been present for years, they still may respond to the *absolute bed rest* treatment (Figure 11). This is not true of duodenal ulcer; in patients having both gastric and duodenal ulcer, the gastric ulcer will heal promptly under bed rest while the duodenal ulcer remains apparently unchanged (Figure 12). An example of a more unusual combination is a benign ulcer and carcinoma of the pylorus (Figure 13). If an ulcer shows such healing, it is an indication of its benign character; if it does not heal it may be due to malignant involvement or it may be due to chronic fibrosis of its margin (Figures 14 and 15); in either event it should be investigated by surgical exploration. It would seem, then, that one field in which roentgen examination can be of aid is in such small malignant lesions which have been brought to light because of early ulceration which has produced

pain. Such lesions are relatively few in comparison with the large numbers of carcinomatous growths.

Mass Surveys

Since early diagnosis, while the cancer still remains a localized lesion, is the only hope of improving our end results in the treatment of the disease with the methods now at hand, and since carcinomas of the stomach are so consistently beyond this stage by the time they produce symptoms, it is evident that some method must be found for their early detection. Mass surveys of the gastrointestinal tracts of healthy individuals, using ordinary fluoroscopic methods, have been proposed as a means of detecting such early lesions, but these have not been very successful. The great success which photofluorographic examination of the chest has met with in the detection of pulmonary tuberculosis naturally suggests the application of this method in mass surveys of the gastrointestinal tract. This method already has been applied to examination of the stomach; 6 to 8 microfilm exposures are made of the barium-filled stomach and those individuals who showed any abnormal finding are submitted to the regular diagnostic fluoroscopic examination. Such efforts have resulted in detection of pathology only about 3 times in 1000 patients over 45 years of age, according to Rigler. This, in view of the enormous expenditure of time, effort and material, to say nothing of the exposure of the radiologist carrying on such work, is obviously impractical as a large scale procedure. Likewise, by far the greatest number of lesions detected by this method are large, hopeless carcinomatous masses. This does not seem to be the solution to the problem.

The results associated with mass surveys of the stomach for cancer could not be compared with those of the chest for pulmonary tuberculosis even if the method were equally successful. Chest surveys were primarily undertaken for the detection of pulmonary tuberculosis, an infectious communicable disease, whereas with stomach surveys the object is to detect cases of cancer early, to better facilitate operative removal, in an attempt to cure the individual patient. *The early removal of a tuberculous patient from contact with others minimizes the spread of the infection and tends to control the disease, whereas in the case of gastric cancer no one is benefited but the individual in whom the disease is detected,* and even this is a doubtful advantage owing to the slight chance of recovery from operative resection. In the case of the tuberculosis survey, fewer and fewer cases will develop subsequently because of the isolation of those detected, and conditions will continually improve, requiring less and less subsequent surveys; in the surveys for carcinoma of the stomach, the discovery of one case would in no way lessen the likelihood of the development of just as many others, no matter how long the surveys would be conducted. Likewise, if there were an established procedure for detection of cancer, how long would such a survey be valid? Surely not more than two or three months. In that case we would be faced with re-examination of all individuals over 50 years of age every three months, which, obviously, would take up the entire time of most radiologists of the country and probably would utilize all the existing hospital and office facilities for this work alone.

Furthermore, tuberculosis attacks the young during the time when they are an economic asset to the country; cancer is an old-age disease which occurs predominantly in aged persons during the period of life when the economic value of their efforts is on the wane or when they have become dependent on others. It is evident, then, that mass surveys of the gastrointestinal tract by our present methods of examination are not the answer to the question of early detection of cancer of the stomach.

There is, however, one bright spot on the horizon. Recently, research has been directed toward brightening the images on the fluoroscopic screen. This has been along two lines: (1) the amplification of the light rays which come from an ordinary fluoroscopic screen through an electrostatic field, causing a more intense image, and (2) a scanning process of amplifying the visual field in a manner similar to television. According to some physicists, these methods hold prospects of brightening the fluoroscopic image to such an extent that it may even approach or equal the detail seen on roentgen films. With such acute perception, it is con-

ceivable that small lesions might be discovered more readily than they are by our present methods, and that earlier detection of cancer of the stomach might become more feasible.

Now, if it is found that carcinomatous lesions actually can be detected earlier by this accentuated fluoroscopic screen image (working models have already been developed), then it might prove worth while to subject a limited age group of symptomless patients to this method of examination. Since the greatest majority of cases of carcinoma of the stomach occur in patients over 50 years of age, and since gastric analysis shows hypochlorhydria or achlorhydria in almost all such cases, it might be of value to submit all patients who enter hospitals for other causes, and who show these findings, to gastrointestinal examination by this new method of intensification of the fluoroscopic image in the hope of finding earlier lesions.

This procedure could best be carried out by utilizing facilities already available in radiology departments of hospitals and in radiologists' offices; this would be the most effective and most economical method. There would not be any need for elaborate photofluorographic units for this purpose as a preliminary screening method of examination of the gastrointestinal tract.

Summary

Our answer, then, to the question, "Is there a method for early diagnosis of carcinoma of the stomach?" is, "No, not with the methods now at hand." But there is a prospect of the development of more precise methods of fluoroscopy which may prove of value in this field.

1. Cancer of the stomach is one of the topmost causes of death in this country today.

2. Its insidious nature often permits it to develop to an advanced stage before it produces symptoms by interference with function.

3. Over-all operative results are woefully deficient as a curative measure.

4. This is undoubtedly due, at least in part, to the lack of early detection.

5. Present roentgenologic methods have advanced almost to their limit in the detecting of carcinomatous lesions early enough so that effective remedial methods can be instituted.

6. Some hope for more precise early diagnosis may be placed in the recent experimental work directed to brightening of the image on the fluoroscopic screen. Working models so constructed would seem to indicate the possibility of the development of a fluoroscopic image having almost as great detail as the roentgen film. If this is attained, the possibility of more precise roentgen diagnosis may become a reality.

REFERENCES

1. Bell, H. G.: The problem of gastric cancer in a university hospital. Surgery 23:351-353, 1948.
2. Coltman, J. W.: Fluoroscopic image brightening by electrical means. Radiology 51:359, 1948.
3. Kirklin, B. R.: Some phases of the roentgenologic diagnosis of gastric cancer. Radiology 24:672, 1935.
4. Kirklin, B. R. and Hodgson, J. R.: Cancer of the stomach; its incidence and detection. Am. J. Roentgenol. 60:600, 1948.
5. Livingston, E. M. and Pack, G. T.: End Results in the Treatment of Gastric Cancer. New York, Paul B. Hoeber, Inc.
6. Moon, R. J.: Amplification of the fluoroscopic image. Am. J. Roentgenol. 59:886, 1948.
7. Moore, S.: Mass roentgenological survey of the gastrointestinal tract to detect cancer of the stomach. Am. J. Roentgenol. 61:470, 1949.
8. Rigler, L. G.: Roentgen examination of the stomach in symptomless persons. J.A.M.A. 137:1501 (August 21) 1948.
9. Sante, L. R.: Intestinal obstruction. Am. J. Roentgenol. 34:744, 1935.
10. Swenson, P. C.: Mass survey of the gastrointestinal tract. South. M. J. 41:108, 1948.

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Gallstone Obstruction of the Small Intestine

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Between 1935 and 1951, at the Mayo Clinic, 9 patients with gallstone obstruction of the small intestine have been treated surgically without a death. The case of 1 of these patients, a man 80 years of age, is presented in detail. The interesting roentgenologic findings in such cases are discussed and details of the surgical treatment are considered.

INTESTINAL obstruction is a common condition. Obstruction of the small intestine due to gallstone is uncommon. Most authors writing on the subject claim that in 1 to 3 per cent of all cases of intestinal obstruction the cause is gallstones;[1,2] this figure is based on cases of obstruction of the large and small bowel encountered at operation or necropsy, including obstruction due to extrinsic inflammatory mass. Hand and Gilmore[3] reported that in 208 of 12,153 cases of intestinal obstruction collected from the literature (that is, in 1.7 per cent) the obstruction was due to gallstones. In the surgical records of the Mayo Clinic for the years 1935 through 1951, a period of 17 years, 9 cases of obstruction of the small intestine due to gallstones were found, which represent about 1.2 per cent of all cases of obstruction of the small bowel for which operation was performed during this period.

In the majority of cases obstruction by gallstones occurs in the seventh decade of life and females outnumber males about 6 to 1. Hence, typically, obstruction of the small intestine by a gallstone occurs in the elderly woman.

Among cases of intestinal obstruction due to foreign bodies, obstruction due to a large gallstone is relatively common. Other less common causes in this category are worms, bezoars, fecaliths, shellac, metals, glass, bone, Murphy buttons, inspissated meconium, latex rubber and casein.

A gallstone may enter the gastrointestinal tract by various routes: (1) A stone which passes through the common bile duct rarely causes intestinal obstruction; (2) a cholecystoduodenal fistula is by far the commonest portal of entry of large gallstones obstructing the intestine;[4] (3) cholecystogastric, cholecystoenteric, and cholecystocolonic fistulas all comprise less common channels; (4) choledochoduodenal fistula is rare, and (5) free perforation of the gallbladder into the peritoneal cavity with subsequent intestinal obstruction by a gallstone is a remote possibility. When a large gallstone has entered the intestine the other, usually smaller, stones can pass freely through the fistula and be expelled without symptoms. The amazing aspect is that the clinical evidence in the history is often scanty or lacking at the time the fistula is formed, and hence the intestinal obstruction itself is the first indication of trouble.

The diagnosis is rarely made preoperatively. In retrospect it will be found that many of the patients had some cholecystic indigestion or colic, or both, related to their cholelithiasis, but

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the paucity of positive clinical findings is striking. In only about 2 per cent of cases of cholecysto-enteric or duodenal fistula does the gallstone cause intestinal obstruction;[5-7] hence, smaller stones are passed readily through the entire intestinal tract. It is estimated that a gallstone must be at least 2 cm. in diameter to obstruct the lumen of the intestine. The point of obstruction is most commonly in the terminal 2 to 4 feet of the ileum, where the progress of the stone is slowed by spasm and definite narrowing, and the size may be increased by multiple coatings of fecal content. It is very uncommon for a gallstone which has passed through the ileocecal valve to produce obstruction in the colon or rectum; however, its slow progress might result in marked enlargement by thick fecal laminas and obstruction at the rectosigmoid narrowing.

It is interesting to note that as early as 1890 Courvoisier[8] discussed intestinal obstruction due to gallstone and ventured the following figures for the incidence of the various sites of impaction of the gallstone: duodenum 22 per cent, lower part of the ileum 65 per cent, ileocecal valve 10 per cent and sigmoid colon 2 to 3 per cent; the commonest site was said to be in the lower 2 feet of the ileum.

There have been reported[9] rare cases in which there were multiple (two or more) episodes of intestinal obstruction due to gallstones (in the same person at different times).

As mentioned, it is the typical picture of obstruction of the small intestine which brings the patient to the doctor, and unless one has a particularly high index of suspicion regarding cholelithiasis as a possible cause there is very little chance that the correct diagnosis will be made before operation. The typical nausea, vomiting, periumbilical crampy pains, central abdominal distention, obstipation, fluid and electrolyte imbalance and failure to improve on the usual intubation and conservative therapy are factors which lead to the necessity for exploration. There may be some tenderness and a questionable mass in the right upper quadrant of the abdomen (over the cholecystic fistula), or at some other site in the mid or lower part of the abdomen (over the impacted gallstone).

The best chance of making the correct diagnosis preoperatively lies in the hands of the radiologist. Several possible findings are of interest: (1) The plain roentgenogram of the abdomen may reveal, in addition to the typical picture of obstruction of the small bowel, an opaque shadow where the gallstone is impacted—positive results are obtained in about 50 per cent of these cases; (2) the plain roentgenogram may show evidence of a cholecysto-enteric (cholecystoduodenal or cholecystocolonic) fistula by the presence of gas or air in the biliary tree[10] (Figure 1), a characteristic finding which is of great importance, but which may be overlooked when the radiologist is concentrating on describing the site and degree of the intestinal obstruction, the position of the nasal suction tube and so forth; (3) if barium has been given orally there may be shadows in the biliary tree, again indicating the presence of a fistula, since the solutions of barium generally used will pass readily through the fistula, and (4) of course, a previous report of a poorly functioning or nonfunctioning gallbladder, with or without cholelithiasis, could be helpful in the diagnosis.

Surgical Considerations

It is important that the surgeon follow closely with the physician the patient's progress during conservative therapy of obstruction of the small intestine. When adequate intubation and supportive measures fail, after a fair trial period, to relieve the situation in these elderly ill women, such patients should be prepared as promptly and as effectively as possible for surgical intervention. The nasal suction tube should be left in place, with its tip close to the site of

obstruction in the ileum; this should obviate any necessity for performing enterostomy above the level of the obstruction either preliminary to, or following, removal of the stone.

On exploration of the abdomen the surgeon does not usually palpate stones in the gallbladder, but there may be a fairly large inflammatory mass surrounding the site of perforation into the duodenum or another part of the intestine; or the fistula may be so well sealed off and quiescent that almost no reaction will be encountered. The distended small intestine can be followed down to the site of impaction of the large gallstone, which is usually firmly lodged in the terminal portion of the ileum, at which point the effects of pressure may make the bowel wall appear more necrotic than it really is. This segment should be handled gently, since the bowel wall at this site might be viable and resection unnecessary. It is advocated that, if possible, the stone be gently dislodged and "milked up"[10] into the distended proximal part of the ileum for a distance of 2 or 3 feet where it is safer to do the enterotomy for its removal. Some surgeons[11-13] feel that this point in technic is of such importance that if the stone cannot be dislodged, as is often the case, it should be crushed through the intact bowel wall and then milked up in fragments. However, patients in whom the impacted stone is removed through an incision made directly at that site seem to get along as well as do those in whom the stone is milked up.

The incision in the ileum over the stone is made in the longitudinal direction, and after delivery of the stone the viability of that portion of the intestine is determined. When the condition of the part is in doubt, the part should be removed; otherwise, the longitudinal incision may be closed transversely in order to prevent narrowing of the lumen, or longitudinally, maintaining adequate lumen. The loop in which this is done should be emptied and isolated by rubber-covered clamps and walled off before the procedure begins. The remainder of the intestine should be checked carefully for other gallstones, which are rarely encountered. The tip of a Miller-Abbott or other double-lumen tube should be threaded close to the site of obstruction (if one is not already there) but not past it, and the tube should be left in place for a few days postoperatively without advancement. The gallbladder and its fistula are best left undisturbed at this operation. It is unlikely that subsequent cholecystectomy is necessary for cholelithiasis, since these gallbladders rarely contain residual stones and the fistula generally closes spontaneously.

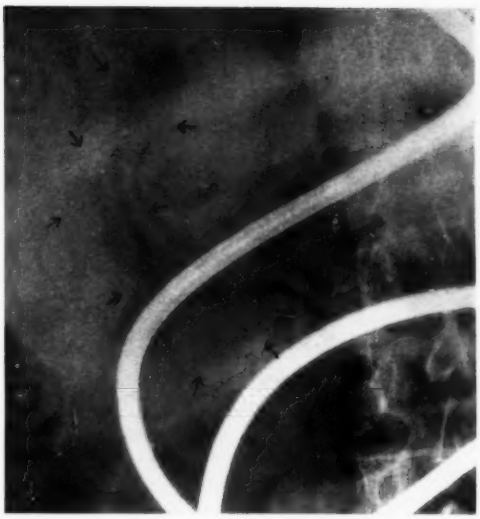

FIGURE 1. Simple roentgenogram of the abdomen made preoperatively for evidence of small bowel obstruction and position of the suction tube; air in the common and hepatic bile ducts was noted in review of many films (in retrospect).

It is rare for second episodes to occur postoperatively. Guthrie and Grant[1] recently reported that a second operation was necessary because of the formation of a hematoma that obstructed the anastomosis made three days previously at operation for intestinal obstruction by a gallstone.

Various rates for operative mortality in this type of obstruction of the small bowel tend to indicate that the chances of survival are little better than 50 per cent;[10-12,14] these mortality rates seem far too high for this benign condition if it is handled correctly. The mortality rates given by Ochsner[15] for intestinal obstruction due to foreign bodies, of which gallstone leads the list, are as follows: enterostomy without diagnosis of obstruction of the small in-

testine, 70 per cent mortality; nonoperative treatment of obstruction of the small intestine, 44 per cent mortality, and laparotomy with or without displacement of the foreign body, 25 per cent mortality. Balch[14] in a review of 295 cases of "gallstone ileus" claimed that only 1 in 8 patients survived if the obstruction lasted more than three days and that 5 in 9 lived if operated on within the first three days; the over-all mortality rate for the entire series was greater than 50 per cent, and death in most cases was due to peritonitis or unrelieved obstruction, or both.

There were no deaths in the 9 patients on whom operation was performed at the Mayo Clinic in the period 1935 through 1951.

Case Report

A man aged 80 years was admitted to the hospital on October 29, 1951. He had had no previous operations or illnesses, other than mild symptoms of hyperprostatism for two or three years. Because of moderate arteriosclerotic changes the patient's memory was poor and no definite history of previous cholecystic or other indigestion could be elicited. He had had no jaundice, colics or abdominal distress prior to the onset of his presenting illness.

On October 27, 1951, 48 hours prior to admission, he experienced sudden onset, after his evening meal, of severe, cramping, periumbilical and lower abdominal pain, which was soon followed by the vomiting of most of his meal. The crampy pain, vomiting and some vague lower abdominal "gurglings" continued every few hours until admission. He had had no bowel movements or flatus for a total of five days before admission. He complained of almost constant soreness deep in the lower part of the abdomen, but no upper abdominal pain.

On admission the patient was found to be a well developed, moderately well nourished, white man of 80 who did not appear critically ill; he was slightly dehydrated and afebrile, with good pulse and blood pressure of 80 mm. of mercury systolic and 50 diastolic. He exhibited moderate generalized arteriosclerotic changes including changes in the central nervous system. The abdomen was poorly relaxed but not rigid and not distended, and presented no masses. There was minimal tenderness in the right upper quadrant and in the lower part of the abdomen slightly to the right of the midline. The peristaltic bowel sounds were within normal limits. The prostate was enlarged and contained one nodule that was suspected of being carcinoma.

The laboratory study of the blood revealed the following: urea, 94 mg. per 100 cc.; leukocyte count, 12,100 per cubic millimeter, 84 per cent of which were polymorphonuclear leukocytes; hemoglobin, 13.6 gm. per 100 cc., and sedimentation rate, 58 mm. in one hour (Westergren). Urinalysis disclosed glycosuria, grade 1; albuminuria, grade 1, and pyuria, grade 1 (all graded on a basis of 1 to 4). A simple roentgenogram of the abdomen showed questionable evidence of early obstruction of the small bowel: there was no comment as to the presence of a gallstone shadow or air in the biliary tree.

The initial clinical impression was early obstruction of the small bowel and questionable carcinoma of the prostate. The so-called enterorenal syndrome was considered. Subsequent investigations revealed volumes of residual urine ranging from 200 to 400 cc., and the diagnosis of benign hypertrophy of the prostate was made. Proctoscopic examination and roentgenologic examination of the colon with the aid of a barium enema were not contributory. Roentgenograms of the stomach and gallbladder were not made.

During the ensuing two weeks obstruction of the small bowel remained complete in spite of temporary periods of relief occasioned by adequate supportive therapy and decompression through a Miller-Abbott tube. Considerable difficulty was encountered in getting the suction tube beyond the pylorus during the first 48 hours, and on one occasion after suction had been well established the patient removed the tube. The concentration of urea in the blood dropped progressively to 30 mg. per 100 cc. with intravenous fluid therapy, and the diagnosis of enterorenal syndrome became more remote. When the suction tube was clamped off for several hours at a time the periumbilical crampy abdominal pain and vomiting returned. Several simple roentgenograms of the abdomen, at intervals of 24 to 48 hours, showed progressively

FIGURE 2a. Impacted gallstone exposed through a longitudinal incision in a segment of the terminal portion of the ileum. b. Gallstone delivered from the site of impaction, without fragmentation. c. Closure of the longitudinal opening in the ileum, by running catgut and interrupted cotton sutures, in the same longitudinal axis, with adequate preservation of the lumen.

more definite evidence of obstruction of the small bowel, with characteristic distended loops and the "stepladder" pattern. At various times physical examination revealed moderate abdominal distention and increased peristaltic sounds. Fluid and electrolyte balance was well maintained and on November 14, 1951, it was decided that the patient's condition was satisfactory enough to permit surgical exploration. The preoperative diagnosis was obstruction of the small bowel of undetermined cause.

On November 15, 1951, abdominal exploration revealed a mass about the size of a golf ball in the right upper quadrant, where the gallbladder, containing no residual stones, was plastered against the duodenum; presumably a large cholecystoduodenal fistula had formed. This site was not disturbed further. In the lower part of the abdomen a loop of distended ileum was followed down to a mass in the right side of the pelvis, at which point a "tumor" was found in the ileum at a distance of about 3 feet proximal to the ileocecal valve. When this loop of ileum was delivered out of the wound it was noted that the small intestine proximally was moderately distended (ileum and jejunum) and that it contained the Miller-Abbott tube which had advanced almost to the site of obstruction; the distal part of the ileum and the colon were collapsed. The mass in the lower part of the ileum was very firm, had caused pressure ischemia of the wall of the intestine where it was firmly impacted, and was correctly considered by one of us (Mayo) to be a large gallstone, before the part was opened. The stone could not be dislodged and hence it was removed through a longitudinal incision made directly over it. The normal color of the ileum returned promptly, indicating satisfactory blood supply, and the incision was closed in the same axis with a running baseball catgut suture and interrupted cotton sutures. The stone, which was intact, measured 4.5 by 3 by 3 cm. No other gallstones were palpated in the gastrointestinal tract. The prostate was considerably enlarged. The abdomen was closed without drainage, and the anus was dilated at the end of the operation. Figure 2 is from color photographs taken by the surgeon at the operation, using the sterile camera devised for that purpose.

Postoperatively the patient made an uneventful and rapid recovery. The Miller-Abbott tube was removed in 48 hours, at which time the patient was passing flatus by rectum. He was ambulating and eating well and was having normal bowel movements by the fifth day, and he left the hospital on the twelfth day after operation. At the time he was dismissed the volumes of residual urine were about 200 cc. (rarely up to 400 cc.). It was suggested that he return in the near future for further study and treatment of the prostatic hypertrophy.

Comment

Obstruction of the small bowel by an impacted gallstone is a serious, even though very uncommon, complication of cholecystic disease with cholelithiasis, and might be advanced as one more indication for cholecystectomy whenever the diagnosis of cholelithiasis is made, even in the absence of symptoms of gallstones. In our case the cause of the obstruction was unsuspected preoperatively. The radiologists, in reviewing numerous roentgenograms postoperatively, found air in the biliary tree in almost every film, of which there were a dozen or more. Barium had not been given orally and hence no opaque medium entered the biliary tree, nor had roentgenograms of the gallbladder been made. We considered giving a small swallow of barium to demonstrate the fistula, in the late postoperative period, but it was deemed unwise to risk embarrassment of the site of recently damaged ileum for the sake of proving an academic diagnosis already established.

The high operative mortality rate claimed for this condition has not been experienced in the 9 cases in which surgical treatment has been employed at the Mayo Clinic since 1935. In spite of the fact that most of these patients are elderly and ill with acute obstruction of the small intestine, they have been well prepared for exploration and all have made remarkably good recoveries, no death having occurred during the operation or early follow-up period.

Undoubtedly the time factor in operating upon some of these patients is of great importance. If the patient continues to become worse while all supportive therapy and decompression measures are considered to be adequate, and if there is a definite area of abdominal tenderness—implying circulatory embarrassment to a segment of intestine—the surgeon should be called to follow the clinical course closely with the physician. Early exploration is the procedure of choice when surgical intervention is indicated.

Further surgical attention to the cholecystoduodenal fistula in our case was considered unnecessary, since the gallbladder contained no residual stones and since such a communication usually closes rapidly. Some readers might believe that this policy would permit subsequent occurrence of similar episodes or the establishment of attacks of so-called ascending cholangitis. If such complications develop in these elderly patients the necessary cholecystectomy and repair of the duodenal opening may be considered at a later date.

Summary

A detailed report is made of a case of obstruction of the small bowel due to a gallstone. A man aged 80 years was relieved by simple removal of the stone through an enterotomy directly over the site of impaction in the lower part of the ileum. The preoperative diagnosis was obstruction of the small bowel of undetermined cause. Postoperative review of the many simple roentgenograms of the abdomen, which had been taken during the previous two weeks while the patient was under medical treatment for intestinal obstruction, revealed air in the biliary tree in most of the films. A cholecystoduodenal fistula had been noted at operation.

REFERENCES

1. Guthrie, Donald and Grant, J. J.: Intestinal obstruction due to a gallstone; a case report. Guthrie Clin. Bull. 21:73-76 (October) 1951.
2. Harris, W. L., McNamara, C. E. and Dardinski, V. J.: Gallstone obstruction of the intestine; a brief review of the literature with report of four cases. M. Ann. District of Columbia 16:422-425, 1947.
3. Hand, B. H. and Gilmore, W. E.: Gallstone ileus; recurrence in one case. Am. J. Surg. 59:72-78 (January) 1943.
4. Marshall, S. F. and Mitchell, B. D.: Intestinal obstruction caused by an impacted gallstone; report of three cases. S. Clin. North America 24:648-655 (June) 1944.
5. Mayo, C. W. and Brown, P. W.: Intestinal obstruction caused by a gallstone. Surgery 25:924-930 (June) 1949.
6. Wakefield, E. G., Vickers, P. M. and Walters, Waltman: Intestinal obstruction caused by gallstones. Surgery 5:670-673 (May) 1939.
7. Wakefield, E. G., Vickers, P. M. and Walters, Waltman: Cholecystoenteric fistulas. Surgery 5:674-677 (May) 1939.
8. Courvoisier: Quoted by Maingot, R. H.,[12] p. 617.
9. Downing, W. L.: Gallstone ileus; report of five cases. J. Iowa M. Soc. 38:95-100 (March) 1948.
10. Hinchey, P. R.: Gallstone ileus. Arch. Surg. 46:9-26 (January) 1943.
11. Bancroft, F. W. and Wade, P. A.: Surgical Treatment of the Abdomen. Philadelphia, J. B. Lippincott Company, 1947, p. 668.
12. Maingot, R. H.: Abdominal Operations. Ed. 2. New York, Appleton-Century-Crofts, Inc., 1948, p. 617.
13. Wangensteen, O. H.: Intestinal Obstructions; a Physiological and Clinical Consideration with Emphasis on Therapy; Including Description of Operative Procedures. Ed. 2. Springfield, Illinois, Charles C Thomas, 1942, pp. 316-322.
14. Balch, F. G., Jr.: Gallstone ileus. New England J. Med. 218:457-462 (March) 1938.
15. Ochsner, Alton: Quoted by Bancroft, F. W. and Wade, P. A.,[11] p. 668.

Ringworm of the Hands and Feet

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Fundamentals of fungous infections of the hands and feet are discussed and illustrative photographs reproduced. The importance of establishing a correct diagnosis is emphasized, as well as the need for utilizing microscopic preparations and cultures before any treatment is undertaken.

I BECAME interested in ringworm of the hands and feet in 1914 and my interest has continued to date—not only in that subject but also in all phases of clinical mycology. Following two and one-half years of intensive study my first paper was read at Detroit before the annual meeting of the Section on Dermatology and Syphilology of the American Medical Association in 1916. Before that paper was read, only 7 cases of this type had been reported in this country. I reported on 65 carefully studied cases. Following the reading and publication of the paper it became almost routine to treat all acrodermatoses as mycoses, and since that time I have been trying to undo the damage I did. I have never known whether I did more harm than good in presenting that first paper.

J. H. MITCHELL

In 1950 I was invited to deliver the Distinguished Lecture in Dermatology before the Section on Dermatology and Syphilology, the title of which was "Ringworm of the hands and feet: Historical review." In that lecture I reviewed the literature from the time the first paper on the subject appeared in 1888 (J.A.M.A. 146:541-546 [June 9] 1951) to the present time.

Identification of the Organism

The importance of arriving at a correct diagnosis before treatment with fungicidal or fungistatic preparations is begun cannot be overemphasized. All too commonly physicians say "You have ringworm of the feet" or "You have ringworm of the hands"; then they institute energetic treatment, thereby in some cases making a contact dermatitis much worse. It is of the utmost importance to make use of microscopic preparations and cultures before taking the chance of producing further irritation of the skin.

The technic of microscopic examination consists of removing the roof of a vesicle or removing scales by scraping, placing the material on a glass slide, covering with 15 per cent sodium hydroxide solution, heating gently and pressing the material as thinly as possible beneath the cover slip.

When vesicles are present, their content rarely fails to give a pure culture of the invading fungus. In the absence of vesicles the

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Differential Diagnosis of Fungous Infections

FIGURE 1. In this photograph showing "athlete's foot" or eczematoid ringworm of the feet are seen the characteristic features of an acute vesicular eruption. The grouped, deep-seated vesicles in the arch of the foot are in various stages of involution and evolution, differing in that respect from toxic eruptions in which the vesicles all will be in the same stage at a given moment and the eruption usually will be symmetric. In this case there was an outbreak of vesicles in June, usually a very moist season in Chicago. This man had had maceration in the fourth interspace for a number of years. With the coming of humid, hot weather he developed this vesicular eruption. The early stages are characterized by deep-seated vesicles and the later ones by absorption of the vesicle content, leaving the brownish roof of the vesicle in which the mycelia can easily be found, as a rule, by means of the sodium hydroxide technic. *E. floccosum* was grown in pure culture.

FIGURE 2. The lack of symmetry, the maceration and the vesiculation seen in the ordinary type of fungous infection are shown in this photograph. One foot or one hand usually will be much more involved than the other, although both almost invariably will be affected to some degree. This case was one of those reported in 1916. The activity on the right foot is much greater than that on the left.

FIGURE 3. Fungous infection, showing a closely set group of vesicles in the arch of the foot of a 30 year old woman. The acute vesicular mycotic lesions developed during hot, humid weather. The patient stated that she had done no gymnastic work or swimming, but that she played tennis occasionally. The vesicles seen are in various stages of evolution and involution. *T. gypseum.*

FIGURE 4. Unusual location of fungous infection of the foot. As a rule we expect to find activity on the sole or on the palm but occasionally it is found on the dorsal surfaces, and this case might have fooled me if I had not been on the lookout for a fungous infection. I might have accepted it as a dermatitis which had been overtreated.

surface should be cleansed with alcohol and the scales planted on the surface of the "proof" medium.

One of the outstanding clinical features of ringworm of the hands and feet is the lack of symmetry as regards the activity of the process. Both feet or both hands may be involved, but rarely to the same degree. Thus, the usual fungous infection differs decidedly from lesions due to *Monilia (Candida)* infections, in which the lesions are usually symmetric (see illustrations).

We are now fortunate in having the Mc-

FIGURE 5. This case of fungous infection on the palms, one of those reported in 1916, was the most severe, acute and symmetric I have yet seen. The entire palmar surfaces were covered with active vesicles of acute onset. The areas from which the material was taken for examination and for cultures can be seen. *E. floccosum* was grown on culture.

FIGURE 6. Toxic eruption on the palms, showing the symmetry and all the vesicles in the same degree of involution and evolution. These differ quite markedly in appearance from the vesicles of fungous origin (see Figure 5). Toxic eruptions of this type are very common these days due to the ingestion of the many drugs having such widespread use.

FIGURE 7. Fungous eruptions may occur on the backs of the hands as well as on the palmar surfaces, and such a case is shown in this photograph.

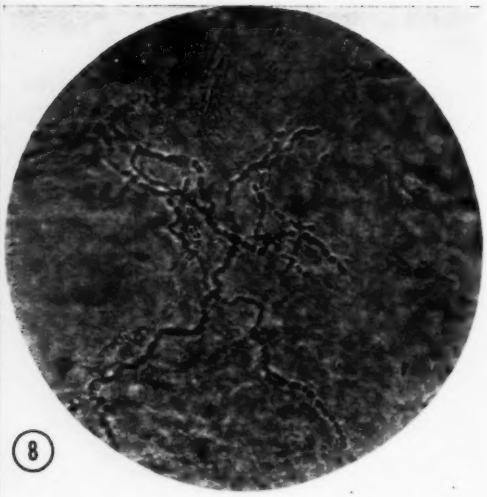
Manus chemical stain because it is selective for the cellulose in fungi and because the organisms can readily be seen with a low power objective. When they have been located with the low power they can then be studied with a high, dry objective.

The staining process is time-consuming but this is more than offset by the ease with which the fungi can be found. The two principal reagents in the staining process are periodic acid solution and the Schiff reagent. The particles of tissue or nail substance must be very small inasmuch as there is no maceration of the material as when sodium hydroxide solution is used.

Culture media are available commercially or can be prepared easily in the office or laboratory. I prepare the media in the office, using a pressure cooker for sterilization.

Sabouraud's medium consists of peptone, glucose, agar and water. This combination is known as the "proof" medium, and on it the colonies will assume a characteristic appearance. However, some of the fungi sooner or later develop degeneration forms when grown on this medium, and when these forms appear the characteristics of the growth are permanently lost. By omitting the glucose, the colony grown on such a medium (known as the "conservation" medium) will not be identifiable, but when transplanted to the "proof" medium the characteristic colony will promptly reappear.

With the "conservation" medium the fungus can be preserved and subcultured indefinitely. Another way of preserving the culture is by covering it with sterile mineral oil; in this way it also can be kept indefinitely and subcultured when desired.



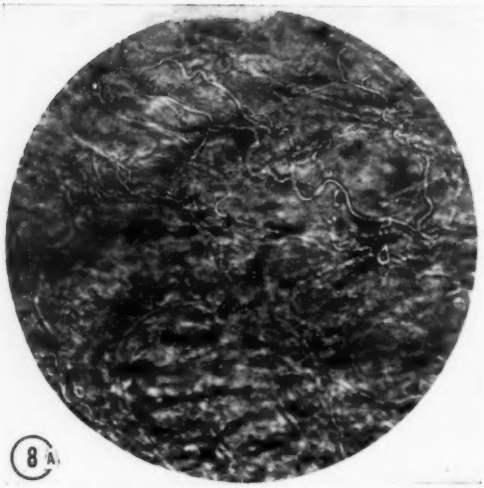


FIGURE 8. Examination of material with sodium hydroxide and the microscope in the ordinary fungous infection due to *E. floccosum* or to the *T. gypseum* group reveals the mycelia without spores, and a tendency toward segmentation in the older lesions. For microscopic examination the roof of the vesicle is removed, inverted on a glass slide and macerated with 15 per cent sodium hydroxide and heat. (Zeiss 1/12-K 10.)

FIGURE 8A. Elastic fibers simulating fungi. When tissue taken for examination contains a portion of the derma the elastic fibers resemble fungi and are frequently mistaken for them by the inexperienced observer.

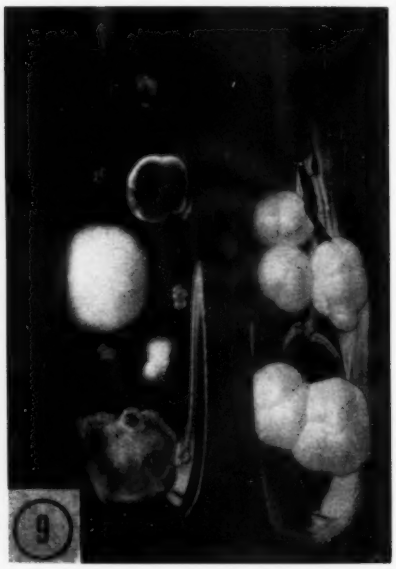
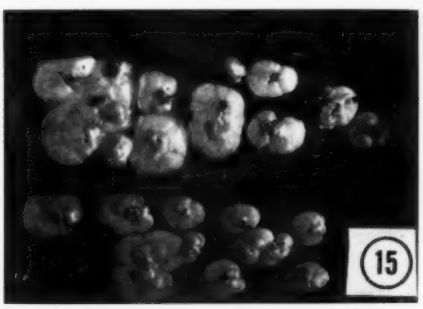


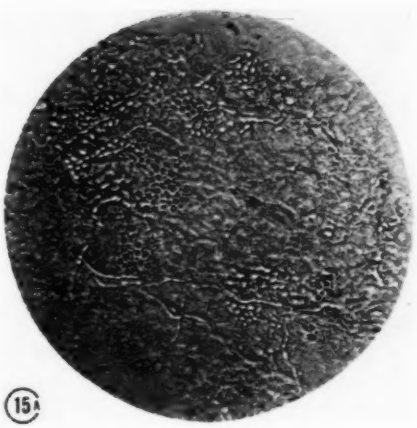
FIGURE 9. Right, *Monilia* infection of the crotch; left, *T. gypseum* infection of the toes. The patient had typical chronic maceration and fissuring between the toes and large areas of typical monilial intertrigo in the inguinal folds.

Nail Involvement

FIGURE 10. Fungous infection of the nail surfaces. Nail involvement creates a very difficult problem which as yet has not been solved. In the type shown—that which begins on the surface of the nails—management is rather easy with salicylic acid in strong plaster or ointment, chrysarobin and iodine in goose grease, and other fungicides, but when the nail bed is involved I become discouraged.

FIGURE 11. A great deal has been written concerning the value of silver nitrate for fungous infections of the nails. In the case of the patient whose foot is shown, the infection had been treated in this manner for three months. I call attention to the fact that there is a thin black streak along the surface of the nail but no penetration of the nail bed. The nail had been cut away, exposing the white nail bed. The organisms in the nail bed were numerous and viable.





Monilial Infections

FIGURE 12. Erosio interdigitalis blastomycetica occurring bilaterally in the third interspace. The patient was a young, obese Jewish woman. This was the first case presented before the Chicago Dermatological Society. The lesions are characterized by their location on the web of the third interspace of the hand, and appear as areas of erosion with a collarette of upturned scales. This lesion does not spread back, as a rule, to the palm or to the dorsum of the hand. Fabry first gave this condition the name of erosio interdigitalis blastomycetica.

FIGURE 13. Monilial infections of the nails are quite different from ordinary fungous infections. They begin with a bolster-like paronychia and then spread later to the nails. The difficulties involved in therapy are even greater than with other fungous infections. Photographs were made on July 25, 1934, when the patient, a 65 year old Jewish man, was first seen. The infection was of many years' duration and there were active lesions in the inguinal and anal folds. Positive cultures were obtainable from any lesion at any time. The condition improved with constant attention and treatment. There was a sharp reaction to OIDIOMYCIN®. A series of injections gave no appreciable therapeutic results.

FIGURE 14. Toenails of the same man whose hands are shown in Figure 13. Note the bolster-like, red, chronic inflammatory process about the nails and symmetric involvement of the nails.

FIGURE 15. Original pure cultures obtained from the toenails.

FIGURE 15A. Photomicrograph of a sodium hydroxide preparation of *Monilia (Candida)*. Mycelia and spores are well shown.

FIGURE 16. A typical example of dhobie itch or washerwoman's itch. The disorder was first given that name in the Pacific tropics because women who had their hands constantly in water were subject to the infection. The man whose hand is shown was a dishwasher in a restaurant. He had his left hand in water and used a mop with his right. Cultures proved the causative organism to be *E. floccosum*. Note that the area involved is at the bases of the third and fourth fingers—a favorite site for palmar infections.

FIGURE 17. This patient had lesions in the same area as had the patient in Figure 16. She had been treated for ringworm with Whitfield's ointment for some time, but already she had a leukocytosis, fever and beginning lymphangitis. She had, in fact, a severe streptococcic infection. I called attention to a group of such cases in a paper read at Cleveland, Ohio, in 1934. Streptococcal infections of the hands and feet may simulate ringworm, and I would like to emphasize that point more than any other. A. Microscopic appearance of *Monilia* in tissue.

FIGURE 18. Bacterids or recalcitrant pustules. This condition is commonly misdiagnosed. Usually there is a chronic infection somewhere in the body, and removing that will bring about some improvement or complete clearing of the pustules. I have found the use of 8 per cent crude coal tar in chloroform more effective than any other external application. The lesions are minute, superficial, sterile pustules, symmetrically placed on the bases of both the palms and soles. The patient shown was a 47 year old man. Duration of the condition, three years. There had been many exacerbations and remissions. All his teeth had been extracted. The lesions cleared with roentgen rays and local applications.

FIGURE 19. In an attempt to correct the harm I had done by presenting the paper in 1916, I read a paper in 1929 on nonmycotic lesions of the hands and feet, and this case was one of that group ordinarily considered mycotic. This was an infectious type of dermatitis; there was no fungus present.

In his early work, Sabouraud reported practically nothing but *Epidermophyton floccosum;* this organism is lemon yellow in culture on "proof" medium and rapidly undergoes degeneration or pleomorphism. The characteristic fruitlike bodies seen in a photomicrograph of a culture mount of *E. floccosum* differentiate this genus at once from all other fungi.

The other organism most commonly found is one of a group known as *Trichophyton gypseum*. Originally this was called *E. interdigitale*. It has been suggested that it is a degenerative form of *E. floccosum*. However, there are a number of closely related organisms in this group.

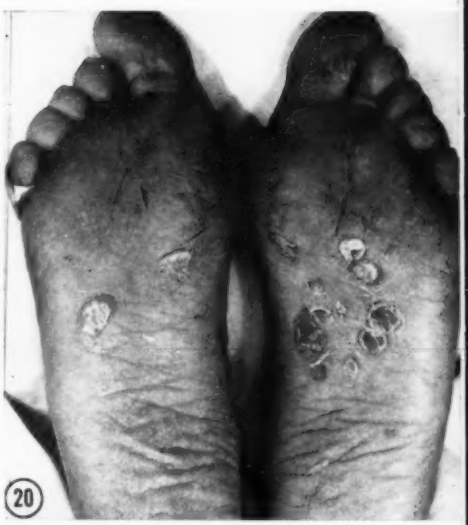
We must guard against mistaking the elastic fibers of the skin for fungi. In years of teaching I have found repeatedly that students and others find the elastic fibers and report them as fungi. In the epidermis of the palms and soles we never encounter the elastic fibers; they are found, however, on the dorsal surface of either the foot or the hand, or in the derma of every part of the body.

It has been stated that two different types

of fungi are never found on the same individual. That statement has been made so many times that I wish to call your attention to the fact that I have observed cases in which two different organisms were found in the same scrapings taken from the lesions of one patient (*E. floccosum* and *T. gypseum*, both from the same field in the crotch). In another case, *T. gypseum* was isolated from the crotch and *E. floccosum* from the toes.

T. rubrum is a real trouble maker in regard to diagnosis and treatment. It produces a port-wine color in the colony and on the reverse side of the culture. The eruption it produces may be quite extensive and may be mistaken for various conditions. I had a patient who was sent to me from Ohio and who had been treated for two years by a psychiatrist for "neurodermatitis." He was well covered with a scaly dermatitis, but there were many islands of normal skin. Cultures and microscopic examinations were made and *T. rubrum* was grown. When the feet are involved they are symmetrically scaly with very little erythema and as a rule no vesiculation. Such cases are very resistant to treatment.

Monilial infections present a microscopic picture quite different from that seen with ordinary fungi. Free spores are seen together with mycelia, and the organisms are easily found; in fact, if they are not found one can be fairly certain that the organism is absent, because it abounds and is very easily demonstrated microscopically and in the culture tube. It is interesting to observe that cultures of *Monilia* are almost always pure, even when taken from vaginal discharges. Evidently there is an inhibiting substance in *Monilia (Candida)* which might bear investigation as a source of an antibiotic.



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Psoriasis

FIGURE 20. Psoriasis is not uncommonly mistaken for mycotic infection. This 50 year old woman had been under observation because of typical lesions on other parts of the body for many years. The plantar lesions had been disregarded by the patient until she was seen by a chiropodist for arch discomfort. She was then told that she had "a terrible case of ringworm which was more contagious than smallpox and which would put her in the hospital in a short time." The chiropodist also said that he had seen thousands of such cases. An elaborate plan of treatment, including use of formaldehyde, was outlined. No fungus was present.

FIGURE 21. This man thought he had a fungous infection of the toes. He applied MYCOSOL® ointment with his fingers and developed a dermatitis on the hands. As the dermatitis spread he applied more mycosol; more mycosol and more dermatitis, until eventually he had mycosoled himself into the hospital.

One point I would like to emphasize more than any other is that streptococcal infections of the hands and feet may simulate ringworm. Whereas fungous infections ordinarily do not cause much trouble, streptococcal infections may be so serious as to endanger life.

FIGURE 22. BUTESIN PICRATE® ointment is also used for treatment of fungous infections of the hands and feet. This man assumed he had a fungous infection of his toes and applied the ointment with his fingers, producing a severe dermatitis up the arms and legs. He also was hospitalized. Butesin picrate ointment is a sensitizer of the worst kind. Many individuals can use it with impunity, but once sensitization has occurred, the dermatitis resulting from its use can be very severe indeed.

Psoriasis is frequently mistaken for fungous infection. Usually psoriatic lesions on the feet are symmetric and not infrequently they are associated with arthropathia psoriatica.

In the accompanying illustrations, the characteristic features of fungous infections are shown, together with conditions which commonly are mistaken for ringworm. Also illustrated are cases in which mistaken diagnoses have resulted in treatment which produced severe dermatitis. In this connection I would like to mention butesin picrate, which is a sensitizer of the worst kind. Although some patients can tolerate it, once sensitization has occurred the dermatitis resulting from its use can be very severe indeed. I have had very unsatisfactory results with SOPRONOL®, DESENEX® and all the rest of the fatty acid preparations. Another danger in treatment is the use of formaldehyde. I advise great caution in its use for any dermatosis. Once dermatitis develops following its use, it never clears.

FIGURE 23. Severe chronic hardening of palms due to applications of formaldehyde for supposed fungous infection of palms.

Case Selection for and Practical Points on the Administration of ACTH; Recent Developments

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This article discusses the changes in emphasis the last year has brought in therapy, the refinement of diagnostic tests of adrenal function, and the newer ACTH preparations and their properties.

THIS paper does not purport to give a comprehensive account of the current status of adrenocortical therapy. A great many practicing physicians today have a good working knowledge of the therapeutic range, the preparations available and the precautions against the common complications. Here will be discussed the changes in emphasis the last year has brought in therapy, the refinement of diagnostic tests of adrenal function, and the newer ACTH preparations and their properties. The emphasis is on ACTH by reason of space, not by reason of the fact that this material is necessarily preferred over cortisone and related products where both are known to be effective.

ACTH Purity, Clinical Effectiveness and Clinical Resistance

When some two years ago a Wisconsin group showed that the same clinical effects could be produced by an intravenous dose of ACTH one-tenth the size of an intramuscular dose, they highlighted the problem. what happens in muscle that diminishes ACTH action?

Every doctor who has watched a patient become resistant under long-term intramuscular therapy or who has taken care of the rare patient who fails to react to intramuscular ACTH at all (despite intact adrenals) has faced this question. Resistance sometimes has been circumvented by a shift of species of the intramuscular ACTH, and it can regularly be circumvented by shift to the intravenous route. Effectiveness comes here at the cost of convenience.

In that preparations of ACTH in clinical use are mixtures of proteins of animal origin and have been shown to be antigenic to animals, it is notable that so few anaphylactoid reactions have been encountered on repeated human intravenous injections. No doubt the ACTH has often treated its own reactions. Serious reactions have been limited thus to the following:

(1) Addison's disease, where there is no adrenal tissue to secrete reaction-blocking steroids.

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Part of the information contained herein is as yet unpublished by the original observers and was obtained by personal communication. Such communication has been greatly facilitated by the annual conference for investigators put on by Armour and Company. All who participated are indebted to Dr. Albert H. Holland, Jr., Medical Director of Armour Laboratories, for making a stenographic transcript of this conference available to them.

(2) Rare instances where massive intravenous ACTH is given to a patient whose own adrenal function has been previously suppressed by long-term cortisone in high dosage.*

(3) Cases in which a sudden massive intravenous dose produces a reaction before normal adrenals have had a chance to respond. (There is a recorded instance of a continuing ACTH infusion blocking the reaction it initially set off.)

In developing a preparation of ACTH many times more potent per milligram of infused material than those in general clinical use, Astwood and his co-workers have provided a solution to some of these problems and a way around others. This further purification, though not resulting in a homogeneous molecular species, has given the profession a product with the following characteristics:

(1) Thus far it has not proved antigenic.

(2) Inactivation in muscle is greatly diminished. Patients refractory to the older preparations intramuscularly respond well to the newer preparation by this route.

(3) The effective intramuscular dose for the improved product is far closer to the effective intravenous dose than is the case for the older preparations. Thus the gel recently made available to the profession incorporating this purer (high potency) ACTH approximates the clinical effectiveness of continuous intravenous infusion.

*ACTH and Tests of Adrenal Function***

One of the first areas of advantage in use of the purified product has been in testing the capacity of the adrenal to respond. The establishment of adrenal function today has wider practical significance than in differentiating between the rare true case of Addison's disease and adrenal hypofunction due to pituitary loss or other causes. For example, a sizeable group of patients throughout the country have been on cortisone therapy for long periods of time, with consequent depression of their own adrenals. As yet no permanent inactivation of adrenals can be ascribed to such therapy. Nevertheless it remains important to establish the continued existence of adrenal function of these patients as they go into their third, fourth, fifth or perhaps later years of treatment. Often they must be removed from therapy and suffer exacerbation of their disease in order to permit the appraisal. They should be informed that this inconvenience is insurance against potential troubles which as yet cannot be evaluated.

Any doctor who has performed many ACTH tests during the last three years will recall patients whose eosinophil counts failed to drop despite his clinical belief that the adrenals were intact. Thus cardiac patients in congestive failure sometimes show a lack of eosinophil drop to intramuscular ACTH yet respond to intravenous ACTH.

A 50 per cent or greater drop of eosinophils four hours after the intramuscular injection of 25 mg. of old ACTH has proved, as a rule, reliable evidence of adrenal function.† The simplicity of this test has made it a good screening procedure. Where the establishment of adrenal function is critical for the patient, it has not proved definitive. A failure of this response to intramuscular injection does not in all instances correlate with absence of adrenal function.

Because of the unreliability of intramuscular injection and because in certain clinical situations other factors may overbalance the effect of adrenal steroids on the eosinophil level, in those instances where establishment of adrenal function is critical in patient management, Thorn and his group have used (1) a 20 mg. dose of old ACTH intravenously on two successive days as the adrenal stimulant

*There exists sparse and fragmentary histologic evidence of serious tissue-allergic sequences in this case so that intravenous administration of *older* ACTH preparations to a patient recently taken off cortisone must be approached with caution.

**The whole problem of indexes of adrenal response to stimulation is undergoing intensive investigation. It is particularly important in the standardization of potency of preparations of ACTH. One of the problems has been that all existing indexes of adrenal response do not parallel one another for a given preparation. Thus, for example, the standard method of ACTH essay (based on adrenal ascorbic acid depletion in the rat) has met the unusual finding of a highly purified preparation which is active from a clinical standpoint and yet gives minimal activity in terms of the rat essay.

†A good many indexes of adrenal function used in the early days of ACTH, e.g., uric acid-creatinine ratio and changes in sodium and potassium balances, have not proved valuable in clinical practice, although they still have some investigative significance.

and (2) changes in 24 hour urinary output of 17-ketosteroids as the index of response. The second day is necessary because some patients who do not substantially increase ketosteroid output on the first day do so on the second.

Definitive as this test may be, two intravenous infusions and three 24 hour urine collections make it a hospital procedure except in offices very well equipped for metabolic work. The availability of the new high potency ACTH gel gives promise of obviating the need for intravenous infusion. Recent simplification (by many groups, notably that of Samuels in Utah) of methods for the measurement of blood and urine 11-oxysteroids gives promise of a four hour test which combines the definiteness of the two day ketosteroid determinations with the brevity of the conventional eosinophil test. Though not ready today for general clinical application, it is under intensive investigation in several different centers.

Specific Areas of Therapy

1. Problem of contraindications—There can be found in the literature of the last five years individual case reports where unexpected serious clinical events occurred during ACTH and/or cortisone therapy. Among these are cardiac infarctions, the development of general hemorrhagic tendencies, perforation from ulcers, wound dehiscence in postoperative patients, the dissemination of tuberculosis from a circumscribed to a miliary form, and the development of a bacterial disease (e.g., meningitis, generalized septicemia) in situations where this would appear unlikely. These events have brought about considerable clinical caution and properly so.

Now every clinician has seen patients with no history of gastrointestinal symptoms or ACTH who learn of their ulcer by sudden hemorrhage or perforation. Not a few young leaders in our own profession, whose cardiac and ACTH-cortisone history is negative, are struck by cardiac infarctions as though out of a blue sky. The interpretation of the significance of these events during hormone therapy needs an adequately validated statistical base line. Such base lines are rarely available. The medical department of Armour and Company has enlisted the aid of many cooperating clinics to put the incidence of these complications on a statistically sound basis. Although final results are not available, a preliminary impression is that these catastrophic events are not sufficiently frequent to warrant any broad dictums forbidding use where real clinical need exists.

For the clinical needs often far overshadow legitimate fear of complication. Sometimes their use is lifesaving (as in acute disseminated lupus); often their use brings merciful, if temporary, relief of suffering. I believe unexpected clinical events should be watched for with special vigilance, vigorously treated and *centrally reported* with a view to ultimate statistical evaluation. The significance for each patient must be decided individually. There are well documented instances of well behaved peptic ulcers when proper medical management is carried out simultaneously with continuous hormone administration for other conditions.

2. Rheumatoid arthritis—A substantial number of workers today are in a position to evaluate almost three years' experience in intensive treatment of rheumatoid arthritis with ACTH and/or cortisone. With a few disagreements the general results are as follows:

(a) The rate of remission on cessation of treatment after a year or more is about 10 per cent, a figure almost identical with that for series of cases untreated by ACTH or cortisone.

(b) Of patients initially selected as favorable candidates for continuous treatment, between one-fourth and one-third seem to show continuing benefit at the two year mark. The remainder (nearly all of whom experienced the usual dramatic relief at onset of therapy) have subsequently fallen by the wayside for a variety of clinical reasons.

In well studied series such reasons do *not* include lack of attention by physician or cooperation by the patient. The occasional corticoid-induced thyroid depression as a cause of failure of clinical response is now well understood and the therapy clear. Some pa-

tients have developed resistance to a given species of ACTH; here change of species or employment of purified ACTH or cortisone is indicated.

The most troubling patients are those who show clearcut progression of their underlying disease despite initial control of pain and other complaints. In these, symptomatic control becomes progressively harder to achieve. A lifelong student of rheumatoid arthritis has said, "When you embark on long, continued therapy (you are) like unto the person who has a bear by the tail. It is no fun for either the patient or the doctor when the doctor lets go of the tail."

Thus it is the present feeling of many workers that a new patient with rheumatoid arthritis is often best handled by intensive use of conventional modalities of treatment, and that when hope of achievement of economic function within reasonable time exists, conventional measures are best continued.

For today's findings throw a conservative emphasis on what the doctor can promise a new patient with rheumatoid arthritis in discussing probable benefits in terms of the costs. They do *not* mean that the adrenal hormones have no value in the treatment of arthritis. Far from it. Patients in the fortunate minority with continued benefit at the two year mark will attest to the lightening of their burdens. It is important to know where this group of patients will stand at three, four and five years. Moreover, ACTH and cortisone appear to be particularly useful in patients with long-standing, crippling arthritis. Here the aim is not suppression of symptomatology; it is simply the achievement of sufficient mobility and freedom from pain so that the patient gains somewhat over his incapacitation—such that he can take to a wheel chair when previously bedridden, eat when previously he had to be fed, and sometimes achieve a limited economic rehabilitation. All the recognized modalities of therapy *in addition to* hormones should be marshaled as indications emerge. ACTH is no contraindication to salicylates, nor cortisone to sound orthopedics and physiotherapy. Again we must emphasize that the success of treatment depends on continuous contact between the doctor and patient—on the search for many apparently minor events which can throw the effectiveness of therapy off (notably infections whose symptomatology is masked thereby).

3. Rheumatic fever—Rheumatic fever is feared for its sequelae of valvular damage, perhaps related to low grade chronicity, and not for its acute course. Recent years tell us that ACTH-cortisone therapy is at least as good as salicylates in suppressing many manifestations of the acute disease. Notably in myocarditis with congestive failure, improvement beyond that expected with salicylates is often achieved.

But to the critical question, "Will ACTH and/or cortisone prevent valvular lesions?" we still do not have a satisfactory answer. With the final results of the international cooperative study in the future, workers in this country have carefully observed patients who, despite initiation of hormone therapy within two weeks of the apparent onset of the disease, have subsequently developed valvular lesions. Thus today's prophylactic emphasis is still on attempts at prevention of recurrent attacks by antibiotic control of beta hemolytic streptococcal respiratory infections.

This emphasis indicates that no one has found out how to prevent valvular lesions with ACTH and/or cortisone. It does not indicate that no one will ever find out how. Some workers, keeping in mind the fact that rheumatic fever can show Aschoff's bodies in the heart on autopsy despite little clinical evidence of activity, feel that courses of treatment have not been long enough. This may be true. Others feel that diagnosis has not been early enough to permit proper beginning of treatment. There is, of course, a practical difficulty in pushing the diagnosis of rheumatic fever too early. Every doctor knows that some children with rheumatic fever have seemed under par in their mothers' eyes for variable periods before the acute manifestations which brought about his visit. Thus the problem of dating the onset of the disease can have intrinsic difficulties as great as the determination of cessation of activity.

The existing findings put a conservative

limit on what the physician can promise the rheumatic fever patient in addition to immediate symptomatic relief in recommending hormone therapy. Certainly, in the very acute attacks, particularly with evidence of myocarditis, this method of therapy is a valuable suppressive tool.

4. Collagen diseases—This term, probably a misnomer, has nearly as many definitions as there are centers engaged in study. Consideration here will be limited to serum sickness, disseminated lupus erythematosus and polyarteritis nodosa as representing the acute and chronic aspects of the clinical spectrum.

Acute and severe sensitivity reactions, whether to drugs (e.g., penicillin) or foreign protein (serum) disease, constitute a most satisfactory field of ACTH and/or cortisone therapy. Relief of symptoms is rapid and dramatic, and because the conditions are usually self limited the patient and the doctor are rarely up against the problem of exacerbation following cessation of treatment.

With regard to acute disseminated lupus, use of these drugs in high dosage has often proved lifesaving. In the more chronic phase of lupus, as in polyarteritis nodosa, varying schedules have been employed in different centers. Some groups believe that continuous therapy with gradually reduced dosage is indicated in both diseases. Others feel that continuous therapy is necessary in polyarteritis, but they try to get their lupus patients off hormone as soon as clinical indications will permit. Again others try to get both lupus and polyarteritis patients off the hormones by gradually decreasing dosage and resuming treatment only when an exacerbation cannot be controlled by other means. My personal preference favors the latter, but clinical data are not yet adequate for final appraisal of these approaches.

As in rheumatoid arthritis, so also in this group of diseases one occasionally sees a patient who, despite initial control of symptomatology, escapes from conventional and then from high dosage, and progresses on to death. In lupus one may encounter clinical sequences and autopsy findings not described in connection with the syndrome in the pre-ACTH era (e.g., a preterminal nephrotic-like stage with postmortem glomerular lesions resembling chronic glomerulonephritis rather than the so-called "wire loops" of lupus). These may be merely examples of many other sequelae which await description in patients who have been carried by hormone therapy into life spans longer than previously were possible.

5. Asthma—The last two years have brought no great change in the original clinical impressions. The hormones certainly have real value as a play for time in the critically ill asthmatic patient. Particularly dramatic results are occasionally seen when decompensation of a cor pulmonale accompanies status asthmaticus in a long-standing asthmatic.

Freedom from symptoms for a patient intensively treated for one week or so still lasts only an average of two weeks after withdrawal, despite an occasional longer period of relief. Lengthening initial treatment lengthens freedom somewhat, but a limit is soon reached. The average length of incomplete remission after some two weeks of therapy still is in the range of two or three months.

Exacerbations have brought some clinicians toward the use of continuous therapy aimed at symptomatic suppression. This carries all the problems seen in continuous therapy of other diseases. It is my feeling that this should not be resorted to unless all other methods have failed and the patient is economically incapacitated by his disease.

6. Allergic dermatoses—The same considerations here apply as in the instance of asthma, though the doses required are far higher and continuity of therapy is usually mandatory for symptomatic control. So sensitive are some patients to diminution in dosage that on daily maintenance doses of some 200 mg. or more of ACTH or cortisone, they can spot a 10 per cent drop in dosage in a matter of hours.

Here the bold use of these hormones has put back into circulation patients previously incapacitated by either self-imposed social ostracism or actual severity of symptoms. How long they can be kept in circulation depends in part on the continuity of the doctor-patient relationship. Special vigilance is necessary to

guard against masked complications of continuous high dosage. Moreover, regular checks for existence of adrenal function should be made in patients where cortisone is so used.

7. Ocular disease—In this area the last two years have brought encouragement rather than limitations to the range of the utility of these hormones. In dealing with the chronic chorioretinitis originally believed to be unamenable to therapy, several groups have achieved significant results using quite high dosages and long periods of treatment. Administration is systemic, for the posterior regions of the eye are not affected by the now common remedy, cortisone eye drops. The usual precautions for high systemic dosage must be observed.

It remains as important in ocular disease as in other conditions to distinguish inflammatory phenomena due to direct infection from phenomena on a presumably allergic basis. If infecting organisms are in the eye, hormone therapy can lessen the penetration of certain antimicrobial agents by decreasing permeability. Particularly in tubercular eye infections, animal evidence indicates that the prognosis can be altered unfavorably.

8. Infectious diseases—All will remember the early findings of Finland and co-workers, namely, that in a patient with pneumonia and pneumococcal septicemia given ACTH but no other therapy, the blood cultures remained positive until the usual time of crisis but the so-called toxic symptoms immediately improved. Thus it became clear that ACTH is no substitute for antibiotics.

Subsequent evidence that ACTH-cortisone, in suppressing ordinary inflammatory processes, not only could greatly confuse diagnosis of localized and general infections but also might aid in their spread gave little impetus to exploration of therapeutic value of the hormones in this area.

Recently a tentative re-evaluation of the initial discouraging appraisal has started. The endeavor is to utilize the so-called "antitoxic" effects as a supplement to all other indicated measures.

Thus in severe, generalized, neglected peritonitis and in acute fulminating meningitis ACTH and/or cortisone therapy occasionally has changed the clinical picture from desperate illness to brightening, renewed interest in surroundings and renewed appetite. It should be emphasized that as soon as the hormone is discontinued, unless the underlying condition has other effective treatment, the patient will become worse than before. The hormone therapy is in essence a play for time to carry out definitive measures.

Whether the time gained pays off in the long run no one yet knows. Experience is not yet large enough to draw valid statistical conclusions. Initial impression is that salvage rates do not seem strikingly better than ordinarily would be expected without hormones. And because of the known effects of these hormones in modifying the inflammatory process in ways which occasionally may be harmful, caution is urged in this usage.

9. Drug addiction—Despite some disagreement between workers in this field, the most definitive studies indicate that treatment with ACTH and cortisone is not a help and sometimes can accentuate withdrawal symptomatology.

10. Surgical uses—The area of usefulness which has emerged for ACTH in general surgery is not too different from that in infectious disease, namely, a play for time against situations which appear overwhelming to the patient. For example, if used in preparing a very sick ulcerative colitis patient for surgery, the immediate improvement has often raised a question whether surgery should be done at all, and yet the subsequent course has demanded intervention.

In preparation for very radical surgery for carcinoma, hormone therapy has seemed to prove beneficial, though accurate statistics are lacking. In massive resections of the liver for malignancy (where hepatic circulation must be temporarily stopped to effect hemostasis), experimental work in Minnesota indicates that a shocklike death is less of a risk with intensive hormone therapy.

Some workers have found that ACTH is of value in controlling cerebral hyperpyrexia in brain surgery, though this postoperative complication is by no means eliminated. In sur-

gery of the pituitary gland, morbidity and mortality rates seem clearly improved by hormone preparation. In management of patients during adrenalectomy, a very high blood level of active adrenal steroid is advantageously maintained by *intravenous* injection of one of the water-soluble alcohols of compound E, if available, or, in the absence of this, of potent aqueous adrenal extract in massive dosage in addition to intramuscular cortisone. By use of such measures adrenalectomy has become a comparatively safe procedure in many centers. Specialized experience is needed for these types of use.

Two points with respect to surgical use need emphasis:

(a) Surgical shock. ACTH and adrenal corticoids are *no substitute for restoration of blood volume*. Though they may act, if given prophylactically, in partial prevention of drop of blood volume *not* due to whole blood loss, the therapy of surgical shock is exactly the same and exactly as emergent as it is without hormones.

(b) Wound dehiscence. The poor healing of wounds received a good deal of early emphasis. Its biologic correlate was the inhibition of fibroblastic repair in certain experimental situations. Certainly many wounds, notably biopsy wounds on patients with various types of disease involving connective tissue, did not heal well.

Though serious dehiscences have been seen in patients receiving ACTH and cortisone, experience has shown many instances of good wound healing even when patients are on long-continued dosages of the hormones. In most clinics, adequate statistical background does not exist for appraisal. Instances have been sufficiently infrequent, particularly when precautions are taken in the suturing of a wound, that I do not feel that the hormones are a contraindication to major surgery where major surgery must be done.

There is one word of warning which relates specifically to cortisone. A patient just off cortisone (who probably has depressed adrenal function) should *not* be operated on without ACTH preparation and *real* evidence of adrenal response. Otherwise the patient carries the temporary operative risk of a patient with Addison's disease.

11. Burns—The great initial promise of ACTH in treatment of severe burns, particularly those which are full-thickness (third degree), has not materialized.

ACTH has proved no substitute for adequate initial therapy for shock, for detailed management of electrolytes or for prevention of such immediate complications of severe burns as ulceration of the gastrointestinal tract. It does not prevent the leakage of proteins through severely damaged capillaries.

Careful analysis has indicated that ACTH does not make possible takes of homologous grafts. Autologous grafting is still necessary in full-thickness burns of extensive nature.

ACTH does not ultimately prevent keloid formation though it may forestall this.

It is true that ACTH gives a cleaner looking burn wound surface, and it is true that in improving the subjective well-being of the patient when this aspect endangers recovery, it has appeared of value. The occasions where it is indicated will be far less frequent than those which can be well handled without it.

MEETINGS AND POSTGRADUATE COURSES

University of Minnesota Medical School, Minneapolis: Continuation course in pediatric neurology, January 26-31, at the Center for Continuation Study. Subjects to be discussed include convulsive disorders, infectious neurologic diseases, brain tumors and subdural hematoma. Guest faculty members will include Dr. Paul C. Bucy, Chicago; Dr. Margaret H. D. Smith, New Orleans, and Dr. Douglas Buchanan, Chicago. Course is under the direction of Dr. Irvine McQuarrie.

Continuation course in ophthalmology for specialists at the Center for Continuation Study, January 19-24. Visiting faculty will include Dr. Kenneth C. Swan; director will be Dr. Erling W. Hansen.

The Treatment of Uterine Hemorrhage

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Treatment of women with uterine hemorrhage will prove most satisfactory if careful diagnostic studies antedate treatment and if physiologic and pathologic changes accompanying the blood loss are properly evaluated.

A. W. DIDDLE

UTERINE hemorrhage, excluding complications of late pregnancy and recent pelvic surgery, may be characteristic of six affections: (1) incomplete abortion, (2) ectopic pregnancy, (3) isolated instances of functional uterine bleeding, (4) uterine cancer, (5) submucous fibroid and (6) certain blood dyscrasias. Uterine hemorrhage is defined here as producing severe anemia or shock, or both.

Two problems, regulation and hemostasis, arise in control of uterine bleeding. Ordinarily, regulation is unimportant other than to eliminate a nuisance to the patient; its correction is generally unsatisfactory and of no value other than psychic. On the contrary, hemostasis is important. Methods used to control hemorrhage vary with circumstances and etiologic factors. Complications may appear from undertreatment as well as from overtreatment if physiopathologic changes accompanying the condition are not evaluated properly.

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Abortions

An abortion is the termination of a pregnancy before extramaternal viability is possible. The earlier an abortion occurs the more likelihood there may be of partial placental separation with incarceration of a loose portion of the placenta in the cervix. Usually the process of placental expulsion involves retroplacental bleeding combined with uterine contractions that shear the placenta from the uterine wall. Contraction of the intermeshed muscle fibers obliterates the maternal sinuses and provides hemostasis, but when placental expulsion is incomplete control of bleeding also is usually incomplete. The smaller the placental mass, the greater the possibility for partial separation. Under these circumstances blood loss may continue as either a slow trickle or a sudden gush.

Slow, continuous bleeding, even though small in amount at any one time, may prove to be hazardous; yet, because the bleeding is slow it is not uncommonly regarded as relatively benign. In contrast, massive acute hemorrhage quickly leads to primary shock and commands prompt attention. Peripheral vasoconstriction initially compensates for blood loss which has been the result of slow

bleeding and tends to camouflage primary shock. Eventually the volume and oxygen-carrying capacity of the blood may prove to be inadequate for physiologic needs. This gives rise to secondary shock, frequently an irreversible condition. Tissues subjected too long to anoxemia suffer permanent damage. Histories of 2 patients are presented to illustrate primary and secondary shock, respectively.

The first patient had onset of vaginal bleeding in the third month of pregnancy. Three hours after the onset bleeding became profuse and the patient was in shock by the fourth hour. In the fifth hour 1000 cc. of whole blood was given. Incarcerated placental tissue was removed from the cervix as the blood transfusion was begun. Bleeding ceased and the patient recovered.

The second patient was admitted to the hospital in premature labor complicated by bleeding due to placenta previa, and in mild shock. Saline and dextrose infusions were administered intravenously. Because bleeding continued and the patient appeared improved the resident physician proceeded to do a cesarean section before blood was available for transfusion. The patient died on the operating table of irreversible shock. Other than criticizing the handling of this woman, it is emphasized that major blood losses necessitate replacement with blood and not with other fluids.

Women with acute bleeding following abortion should be hospitalized for treatment. Initially a blood count is made and blood cross matched for transfusion. This blood is either given promptly or held in reserve, depending on the circumstances. Those women with a hemoglobin level of 10 gm. or less should be transfused. The cervix is visualized with aseptic precautions, and if fragmented placental tissue is lodged in the cervical canal, the tissue is removed with sterile ring forceps to prevent further loss of blood. Simultaneously, ergonovine or METHERGINE® 0.2 mg. is given intravenously. If the cervix is dilated by a nonfragmented embryonic mass, instrumentation should not be done until operating room facilities are available, since one may precipitate uncontrollable bleeding. There is no brief held against those who empty the uterine cavity by operative procedure in non-infected patients; however, it frequently is impossible to recognize the patient with potential infection, especially if she is afebrile when first seen. For this reason it is desirable to delay invasion of the uterine cavity until the patient has been afebrile 24 to 48 hours.

Excessive loss of blood occasionally may necessitate invasion of the uterus regardless of infection. The gravid uterus is emptied carefully to preserve the normal leukocytic barrier in the uterine wall. If the cervix is sufficiently dilated, finger curettage is preferred over the curet to strip the uterine wall. If instrumentation is required, a large curet or ring forceps is used. Packing of the cervix is seldom necessary; continual bleeding after curettage commonly indicates that placental tissue still remains in the uterus.

Treatment with antibiotics will not supplant the measures previously mentioned to combat infection. For that reason their routine administration or promiscuous use is unjustified. The well controlled study made by Jennett[5] showed that antibiotics and chemotherapy are usually unnecessary except in some instances of criminal and septic abortion, especially where repeated attempts were made to induce miscarriage. Penicillin is preferred to the sulfonamides since reactions to the former are less common and it is generally more effective against a greater number of pathogens. Only occasionally is the use of some of the newer antibiotics advantageous.

Ectopic Pregnancy

Symptoms produced by ectopic pregnancies are commonly atypical and misleading. The most consistent findings are a history of relative sterility, spotting of blood at the time of the last expected menses and abdominopelvic pain before the end of the eighth week of gestation. The time and amount of the first intra-abdominal bleeding usually depend on the size of the vessel eroded and the site of the displaced trophoblast. Usually if the pregnancy is in the isthmus of the tube, rupture occurs by the sixth week of preg-

nancy; if it is in the interstitial portion, the rupture will occur after the eighth or tenth week or later, and if the pregnancy is in the ampulla or body, the rupture will occur from the fourth to the eighth week.

Curettage may prove helpful occasionally to differentiate between incomplete abortion and extrauterine pregnancy. In all instances where diagnosis is equivocal culdocentesis is done for old blood; old blood will not clot, while fresh blood clots in less than six minutes. This diagnostic procedure is made in the midline through the posterior fornix, since vascular areas or some vital structure may be penetrated if made elsewhere. In afebrile patients cul-de-sac puncture aids in differentiation from pelvic or tubo-ovarian abscesses. Under any circumstance, when extrauterine pregnancy is suspected, the patient is hospitalized, blood is cross matched for transfusion and diagnostic studies are pursued without delay. Failure to follow such a plan can be disastrous or even fatal to the patient.

If the woman is not seen until rupture has occurred, treatment is first directed toward combating or preventing shock. It is conceivable that one might sometime be confronted with a patient in progressive shock without a supply of blood for transfusion being available. Then it is necessary to open the abdomen, ligate the bleeding vessel and utilize blood from the peritoneal cavity for transfusion purposes. If blood from the peritoneal cavity is not needed for this purpose, its removal is unnecessary.

It is not always advisable to fully replace major blood losses in a short period of time. Prompt replacement of the entire loss may overload the circulatory system and give rise to pulmonary edema and shock of a different sort. Peripheral vasoconstriction occurs with hemorrhage. If blood or fluids are replaced too rapidly, the pulmonary capillary network becomes engorged, encroaches on the alveoli and actually decreases the aerating surface within the alveoli.

The clinical picture is represented in the discussion of a third patient, who had pelvic surgery. Brisk bleeding occurred at one time during the operation. Moderate shock followed which was counteracted with rapid blood transfusion. Later, in spite of satisfactory hemostasis the blood pressure fell and signs of pulmonary edema appeared. The anesthetist had difficulty both in maintaining surgical anesthesia and in preventing further shock. Nearly 1800 cc. of blood was lost during the operation. During the same period 2000 cc. of whole blood was administered. Postoperatively this woman showed signs of water logging for 24 hours. This story could be repeated many times. On the battle field during World War II, many men were killed by overtreatment with plasma and blood with the thought they were being undertreated rather than overtreated.

Functional Uterine Bleeding

Functional uterine bleeding arises from hormonal imbalances involving disturbed ovarian function. Occasionally this bleeding is severe, as in menorrhagia, metrorrhagia or menometrorrhagia. Sensible treatment of functional uterine bleeding requires knowledge of menstrual physiology and the probable action of the endocrines.

There are four theories as to the cause of menstruation.[7] Edgar Allen advanced the idea of estrogen withdrawal. F. L. Hisaw added evidence that the precipitating factor may be progesterone. Others point out that withdrawal of either estrogen or progesterone, or both, may cause bleeding. A fourth assumption is that menstruation is initiated by an unknown factor "X" that selectively produces strong vasoconstrictor action on the coiled endometrial arteries causing ischemia that leads to necrosis. Diapedesis of blood appears when the arterioles reopen. This action is confined to the junction of the superficial two-thirds and basal one-third of the endometrium.[6] Hyperemia apparently precedes the menses due to acetylcholine evoked by the estrogens.

Estrogens and progesterone have specific effects which are in part antagonistic and in part complementary. Estrogens stimulate growth and muscular activity in the genital tract and encourage proliferative growth of the endometrium, but ostensibly inhibit pro-

duction of the follicle-stimulating hormone of the pituitary and are antagonistic to action of progesterone on uterine muscle. Progesterone stimulates development of the secretory endometrium, but inhibits production of the luteinizing hormone of the pituitary and antagonizes the stimulating effect of estrogens. These endocrines affect the ovarian function by way of the pituitary. Evaluation of their use entails consideration that functional uterine bleeding is commonly subject to spontaneous remission without treatment.

The effects of neuropsychodynamic factors also merit serious consideration from a pathogenic viewpoint.[1] For example, a middle-aged, single woman experienced metromenorrhagia of 10 years' duration. Unilateral oophorectomy, repeated curettage and use of various endocrines gave only temporary relief. During this 10 year period a clandestine affair was carried on with a married man. Each time social complications occurred metromenorrhagia with other functional complaints appeared. Eventually the man secured a divorce and married the patient. Her menstrual upsets ceased thereafter.

Severe functional uterine bleeding produces anemia which ostensibly may promote more bleeding. Under these circumstances it is beneficial to replace blood elements by 500 cc. blood transfusions daily until the hemoglobin level reaches at least 11 gm. Usually, curettage not only will temporarily curb the bleeding so that other measures may be instituted, but also may be of diagnostic value.

It is logical to give endocrine treatment in accord with present day knowledge of menstrual physiology; however, indiscriminate treatment is often worse than none at all. The age of the patient may be a determining factor. Improvement in mental and physical hygiene and nutrition, and the use of thyroid where basal metabolic and blood cholesterol studies show hypothyroidism frequently are most helpful in the adolescent girl or in the woman in middle-menstrual life. Endocrine therapy for women in the menopause is usually not considered the treatment of choice; these women are treated with irradiation or total hysterectomy. All patients 25 years of age or more are subjected to fractional curettage or repeated cytologic studies before any definitive treatment is given. There are those who would disagree with this low age limit but in the last three years I have personally treated 8 women under the age of 30 years with uterine cancer, 7 with invasive cervical carcinoma and 1 with endometrial sarcoma. In 2 patients the lesion arose within the canal, and the portio of the organ appeared normal.

Periods of enthusiasm for hormonal treatment come and go. Estrogen and progesterone are generally administered in one of two ways: (1) The cyclic method is employed giving estrogen the first 10 to 15 days of the menstrual cycle, and estrogen and progesterone together the next 10 days, or (2) either estrogen or progesterone is given in decreasing doses over a short interval prior to or during menses, to preclude excessive, prolonged bleeding.

Androgens act on the pituitary in the same manner as do estrogens. These are preferred to estrogens because withdrawal bleeding is less likely to occur. On the other hand, masculinizing effects may appear with excessive doses and prolonged use. It is stressed that the three groups of hormones previously discussed usually constitute substitution rather than curative treatment. If used they should be administered orally. There is seldom an excuse to give them hypodermically. Serum and urinary gonadotrophins and pituitary extracts seldom prove satisfactory because purification for injection destroys the active ingredients. Also, Brown and Bradbury's work[2] indicates that effective daily dosages of chorionic gonadotrophin probably should range from 5000 to 20,000 I.U. However, the scarcity of this substance limits its use to experimental studies.

Irradiation of the ovaries for treatment of menstrual disturbances is usually confined to patients in the menopause. Its use in younger women is inadvisable. Even the experienced radiotherapist commonly finds it difficult to determine roentgen dosage that will depress but not destroy ovarian function. When bleeding occurs in women of menopausal age six

months or more after irradiation, some clinicians recommend total hysterectomy, particularly if previous endometrial biopsies show hyperplasia. However, the issue is controversial as to whether or not these women in later years more often have endometrial carcinoma than do untreated women of comparable age.

Mild functional uterine bleeding is too often the excuse for hysterectomy, especially in the young or middle-aged woman. Only patients who acquire chronic anemia and fail to respond to less drastic measures are justifiably subjected to the procedure.

Cancer

Uterine cancer is commonly the cause of severe anemia from continual blood loss which may be so severe as to produce cardiac failure resulting from hypovolemia as was the case in another patient. This woman was admitted to the hospital bedridden with cardiac failure, dependent edema and anemia due to chronic vaginal bleeding that proved to be from endometrial carcinoma. Before treatment for the cancer was administered repeated blood transfusions were given to raise the hemoglobin level from 4 gm. to normal. After a couple of weeks the cardiac decompensation disappeared, as did the edema.

Severe terminal hemorrhage not uncommonly occurs with advanced cervical cancer, especially the endophytic type. Hemorrhage results from erosion of the cancer into a branch of the uterine artery. In this instance treatment with vaginal packing is of little value, while electrocoagulation may be lifesaving. Subsequently irradiation is employed in untreated patients to preclude further extension of neoplastic growth and to curtail further loss of blood. Even women considered incurable when first seen are treated to minimize this complication. If these methods fail, ligation of both hypogastric and ovarian arteries is done provided the patient is a satisfactory surgical risk. However, this procedure sometimes fails to keep bleeding in check, particularly in the previously irradiated patient, because collateral circulation may be re-established in a few weeks or months. Exenteration as performed in some large cancer centers is still in the experimental stage and is not adapted to the average hospital.

Submucous Fibroid

Bleeding from a fibroid uterus is usually attributed to endocrine disturbances rather than to the fibroid itself and is generally chronic rather than acute. Submucous nodules commonly increase the bleeding surface and this projection above the endometrial stroma may preclude normal regeneration of the endometrium over the tumor and cause prolonged bleeding. The uterus frequently exerts expulsive pressure on pedunculated tumors that protrude into or hang through the cervix. This produces pressure atrophy of the endometrium, hampers nutrition and leads to necrosis of the mass. In patients who are poor surgical risks pedunculated tumors hanging from the cervix may be severed at their base. The stumps quickly retract with little bleeding. Decision may be made later whether or not more radical surgical measures are needed. If hysterectomy is done, total removal of the uterus is the procedure of choice. There is seldom an excuse to leave the cervix; as long as subtotal hysterectomy continues to be done we shall have the potential problem of cancer of the cervical stump.[3]

Blood Dyscrasias

Least common of the causes of severe uterine bleeding are certain blood dyscrasias such as aplastic anemia, acute leukemia and thrombocytopenia. Under these circumstances bleeding generally occurs from a disturbance in the clotting mechanism and is usually observed at the time of a regular menstrual period or with abortion.[8] Several blood transfusions may be required with each bleeding. Although treatment is directed at the primary disease, castration by irradiation may be necessary to curtail blood loss through the genital tract. Any woman who *walks* into an office with uterine bleeding and a red blood cell count below one million should be suspected of having a blood dyscrasia.

An example of uterine hemorrhage due to leukemia and the problem of treatment is il-

lustrated by the case of a 34 year old woman who supposedly had a spontaneous abortion in the second month of pregnancy. She had a severe hemorrhage and received 2500 cc. of blood in two days. Two months later, at the time of the first postabortal menstrual period, bleeding was so severe that hospitalization was necessary. On admission, the red blood cell count was 1.3 million and the white blood cell count was reported as normal. She was given two pints of blood. Since uterine bleeding continued without obvious cause, bone marrow studies were made. These disclosed aleukemic leukemia. In spite of treatment directed to the primary disease, hemorrhage occurred with subsequent menstrual periods, necessitating repeated transfusions. To control this blood loss the patient was eventually castrated by irradiation.

Summary

Fritz Irving,[4] analyzing the progress in obstetrics and gynecology during the 50 year period from 1900 to 1950, was of the opinion that blood transfusion was the most beneficial addition to our gynecic armamentarium. The blood bank with incorporation of Rh determinations made blood available quicker and its administration safer for more people than ever before.

Hemorrhage is the major complication of abortion and ectopic pregnancy and occasionally is a complication of cervical cancer and certain blood dyscrasias. Although not always lethal, chronic bleeding may occur and produce severe anemia and hypovolemia in women with endometrial cancer, functional uterine bleeding and submucous fibroid. Prompt examination and hospitalization of the patient for treatment will help to prevent loss of blood and fatalities. Blood transfusion should be utilized freely.

Patients with abortion should be examined to make sure the abortus is not caught in the cervix. If it is, careful, quick removal is effected. There is no evidence to support the theory that proper examination stimulates the process of abortion; without examination much time and blood may be lost. Ectopic pregnancy is an emergency. Immediate surgical treatment is given after the diagnosis is established. No procedure other than hemostasis is permissible unless the patient's condition is excellent.

Hemorrhage with functional uterine bleeding and submucous fibroid is not uncommonly debilitating and may lead to severe anemia. Chronic bleeding may incapacitate a woman longer than either abortion or ectopic pregnancy. Treatment frequently depends on the age of the patient and must be individualized. Unfortunately, severe bleeding with uterine cancer and certain blood dyscrasias is generally a terminal complication. On the contrary, uterine hemorrhage may be the first sign of thrombocytopenia, leukemia or aplastic anemia. Radical surgical attack for uterine cancer and castration for the blood dyscrasias may be required for hemostasis. The data previously given indicate the importance of careful diagnostic studies among women with abnormal uterine bleeding.

REFERENCES

1. Blaikley, J. B.: Menorrhagia of emotional origin. Lancet 2:691-694 (October 15) 1949.
2. Brown, W. E. and Bradbury, J. T.: Study of physiologic action of human chorionic hormone: Production of pseudopregnancy in women by chorionic hormone. Am. J. Obst. & Gynec. 53:749-757 (May) 1947.
3. Diddle, A. W. and Bennett, T. R.: Carcinoma of cervix in an urban population. Am. J. Obst. & Gynec. 55:669-675 (April) 1948.
4. Irving, F. C.: 50 years of medical progress—medicine as a science: Obstetrics. New England J. Med. 244:91-100 (January 18) 1951.
5. Jennett, R. J.: Studies of abortion; effect of sulfadiazine and penicillin on clinical course of infected abortion. M. Rec. & Ann. 42:548-550 (July) 1948.
6. Markee, J. E.: The morphological and endocrine basis for menstrual bleeding. In Meigs, J. V. and Sturgis, S. H.: Progress in Gynecology. New York, Grune & Stratton, 1950, vol. 2, chap. 5, pp. 63-74.
7. Plass, E. D.: Functional menstrual disturbances. J. Missouri M. A. 37:418-420 (October), 1940.
8. Wolff, J. R. and Limarzi, L. R.: Blood disorders associated with pregnancy. Am. J. Obst. & Gynec. 51:447-466 (April) 1946.

Lupus Erythematosus

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Lupus erythematosus, one of the more common diseases of the skin, occurs as three types: (1) chronic discoid; (2) subacute, and (3) acute. Systemic symptoms and signs seldom occur in the chronic form, but are always present and may be severe in the subacute and acute types.

LUPUS erythematosus is one of the more common diseases of the skin. Originally it was considered to be a variant of or related to lupus vulgaris, and hence it was thought to be caused by the tubercle bacillus. This opinion is no longer tenable, although the etiology is still unproved. Lupus erythematosus occurs in three forms: (1) the chronic discoid type, which has little or no effect on the general bodily economy and in which the skin lesions are most often present on the face and neck, although they may be more profusely distributed; (2) a subacute type, and (3) an acute type, each of the latter being accompanied by systemic symptoms. In the acute type these symptoms may be very grave and the disease is often fatal. The chronic discoid type occurs equally in both sexes and at all ages, but the other types appear predominantly in young women, the ratio of women to men being 10 to 1. Pathologically there is damage to the mesenchymal structures, particularly of the kidneys, and thus lupus erythematosus is classed as one of the collagen diseases along with rheumatoid arthritis, scleroderma and dermatomyositis. In the acute type there may be vegetations on the heart valves. Stress is an important factor in all three forms of the disease.

C. W. LANE

Figures 1 and 2 demonstrate the classic butterfly distribution of the chronic discoid type. The early papular lesions increase in size to form nodules and/or coalesce to form the flat-topped, raised patches and plaques of irregular shape and size. The surfaces are capped with adherent gray scales. When these scales are removed, there can be demonstrated the follicular plugging typical clinically and pathologically of lupus erythematosus. The lesions are usually bright red to purplish red in color.

In this location the eruption may be confused with seborrheic dermatitis, rosacea and psoriasis. Seborrheic dermatitis occurs as greasy, scaled lesions of orange-yellow color and is usually accompanied by scaling of the scalp, eyebrows and ears. Rosacea is limited to the midface and is manifested by dilated blood vessels with papular and pustular

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FIGURES 1 and 2. Classic butterfly distribution of chronic discoid type of lupus erythematosus.

FIGURE 3. Group of papular lesions in the left malar region.

FIGURE 4. Dissemination of the chronic discoid type of eruption over the upper part of the back.

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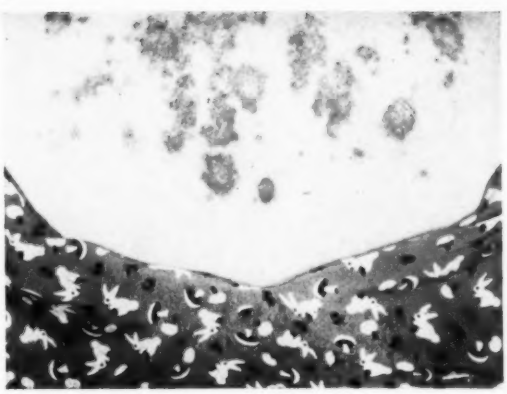

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lesions, but no plaques. Psoriasis occurs rarely on the face.

The patient in Figure 3 has only one group of papular lesions in the left malar region. This type, in which there is no scaling and the eruption is localized, may resemble the eruption of sarcoid of Boeck, although the latter is more granulomatous and manifests a persistent brown color on diascopic pressure.

A dissemination of the chronic discoid type of eruption over the upper back is illustrated in Figure 4. The central scaling and clearing with more pronounced activity of the raised margins is typical. On the trunk and on the scalp the eruption may be misdiagnosed as psoriasis, although the scales are not as silvery or as thick. Unlike psoriasis the lesions of lupus erythematosus result in scarring, and if hairy regions are involved permanent alopecia occurs.

The vermilion borders of the lips and the oral mucous membranes are frequently affected. In the case of the patient in Figure 5, the lip is thickened and covered with a dry, adherent scale as though painted with collodion. It is also dotted with several excoriations. In Figure 6 is seen a solitary thickened, white patch which closely resembles leukoplakia. Similar patches in the mouth are quickly denuded or ulcerated due to moisture, heat and friction. If the mucous membrane eruption is accompanied by skin lesions the diagnosis is not too difficult, but when the disease occurs primarily on or is limited to the lips or mucous membranes it is often misdiagnosed.

The end result of the chronic discoid type is a scarring as is demonstrated on the face and lips of the patient in Figure 7.

The subacute type is shown in Figure 8 and the acute form in Figure 9. The eruption varies from a faint, almost unnoticeable blush to a bright, diffuse reddening, or it may be

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FIGURE 5. Involvement of the vermilion borders of the lips and the oral mucous membranes.

FIGURE 6. A solitary thickened, white patch which resembles leukoplakia.

FIGURE 7. End result of the chronic discoid type, illustrated by the scarring on the face and lips.

absent entirely. The butterfly distribution may or may not occur and the erythema is at times widely or sparsely distributed over the neck, trunk and extremities. The upper chest (Figure 10) and the dorsa of the fingers (Figure 11) are frequently involved. The eruption may be confused with erysipelas, sunburn or actinic eruption or dermatomyositis.

The subacute and acute stages are distinguished by the number and severity of the accompanying symptoms and the laboratory findings. The patient with the subacute type complains of being weak and tired, of headache and arthralgia. There are usually a low grade fever, a mild albuminuria and a moderate leukopenia. All these symptoms are increased in the acute fulminating type, which may be rapidly fatal. In addition these patients usually have a pronounced reduction of the leukocytes, an increased sedimentation rate, a reversal of the serum proteins and pronounced albuminuria with casts and erythrocytes.

A most important advance in confirming a diagnosis of the acute type was the discovery of the lupus erythematosus phenomenon. This almost specific reaction can be demonstrated when the lupus erythematosus factor is present in the gamma globulin fraction of the serum of patients ill with lupus erythematosus. A positive result occurs when bone marrow or serum of the sick patient is mixed with normal white blood cells (obtained from a donor), is allowed to stand, is centrifuged and then is stained. Three findings are necessary to produce the lupus erythematosus phenomenon: (1) clumping of the white blood cells; (2) rosette formation by the white blood cells, and (3) the presence of a lupus erythematosus cell. In my experience the test has been positive in 95 per cent of the acute and about 50 per cent of the subacute cases, but has been negative in the chronic discoid type.

Treatment

No particular modality of treatment is successful in lupus erythematosus. Since many patients react poorly to sunlight all should be warned to protect themselves as much as possible from the actinic rays. If unable to avoid

FIGURE 8. Subacute form of lupus erythematosus.

FIGURE 9. Acute form of lupus erythematosus.

FIGURE 10. Involvement of the upper part of the chest.

FIGURE 11. Involvement of the dorsa of the fingers.

such exposure, wide-brimmed hats, parasols and topical preparations (lotions and ointments) which screen out the sun's rays should be employed.

Orally, drugs which have been employed with some success in the chronic discoid type are BISTRIMATE® (bismuth-sodium-triglycollamate), the sodium salt of para-aminobenzoic acid, and the salt of pantothenic acid along with iron, liver and vitamins.

Parenterally, injections of crude or refined liver are often beneficial. The most effective treatment has been the intravenous injection of the gold salts, preferably gold sodium thiosulfate. If this fails, intramuscular injections of bismuth or bismuth and arsenic may be tried.

Particularly resistant localized patches can be removed at times by the application of liquid oxygen, liquid nitrogen and carbon dioxide snow.

The most important therapeutic procedure for the subacute and acute types is complete bed rest. Overexertion, undue excitement and stimulation must be avoided. Sedation, vitamins, iron and liver are indicated. Transfusions may be lifesaving but should be given with extreme caution. The heavy metals must never be given in these stages. Adrenocorticotropic hormone and cortisone have been most important therapeutic aids. Some almost moribund patients have been saved by heroic dosage (1000 mg. daily of cortisone), but in the subacute and severely ill patients the ordinary dosage of 200 or 100 mg. daily will often abort the attack. As with all other diseases in which they have been used, these drugs are not curative, but in a disease in which there formerly was so little hope for recovery they offer a happy though temporary solution. Despite their use the prognosis in the subacute type, and particularly for the acutely ill patient, is grave.

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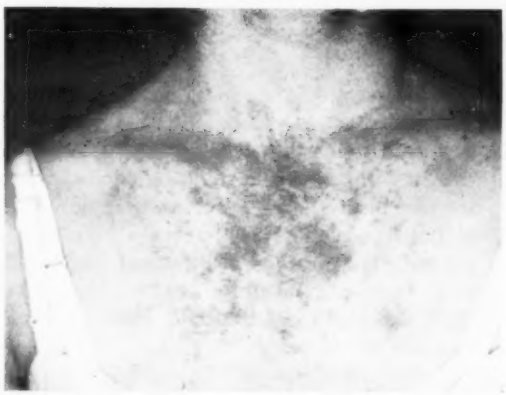

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Spontaneous Rupture of the Nonpregnant Uterus

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A case report is given of a spontaneous perforation of a nonpregnant uterus caused by extreme stenosis of the cervix with subsequent accumulation of secretions, infection and necrosis of the wall.

THE following case report is given because the condition involved is quite rare—so rare, in fact, that it is not even mentioned in Novack's "Textbook of Gynecological Pathology." There are, however, a few scattered case reports in the literature. The clinical picture, while rather characteristic, is also rather unknown, a circumstance which decidedly operates to the detriment of the patient.

Case Report

Chief complaint—A 72 year old white woman presented herself with the complaint of constant vomiting.

Past history—Little could be elicited from the past history. The menopause had occurred at the age of 45. Eight months before the present illness, when the patient had been seen by a physician in another town, her chief complaint was vaginal bleeding. She was advised to report to a cancer clinic for dilatation and curettage, but she refused to do so. For the last four months she had had intermittent attacks of vaginal bleeding and had complained about abdominal pains.

Her present acute illness began with a chill. After three days, vomiting started. There had been no bowel movement for three days.

Physical examination—Physical examination revealed a dehydrated, elderly woman whose temperature was 103° F., pulse 100, respiration 24, blood pressure 140/60. The examination of the head and chest was negative. The entire abdomen showed definite rigidity and was distended; no bowel sounds could be heard. There was some general rebound tenderness with the greatest area of tenderness localized in the right lower half of the abdomen. Vaginal examination showed a moderate amount of foul-smelling vaginal discharge. The cervix was small and atrophic, and inspection showed discharge and bleeding from the cervical os. On pelvic examination nothing could be felt through the abdomen because of pain and rigidity.

Laboratory findings—Red blood cell count was 4,700,000, white cell count 6700. Urine was clear, with 10 white cells per high power field; acetone +1. Kahn test was negative. X-ray report was as follows: "There is dilatation of the colon. There is some free peritoneal fluid. There are some loops of small bowel distended by gas. This is highly suspicious of paralytic ileus probably due to obstruction in the region of the lower jejunum or proximal ileum."

On the second hospital day, operation was performed. There was general peritonitis with purulent exudate on the small intestines. There was a moderate amount of purulent fluid present. The serosa of the intestine was

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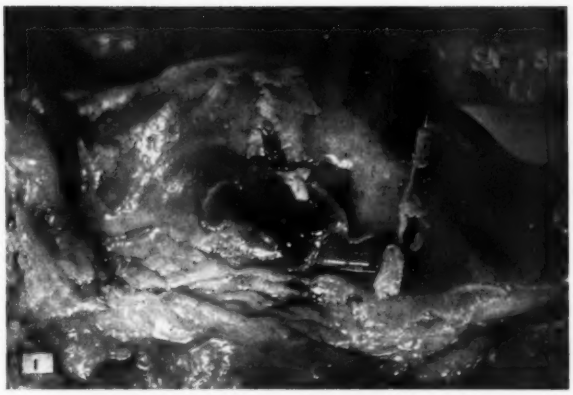
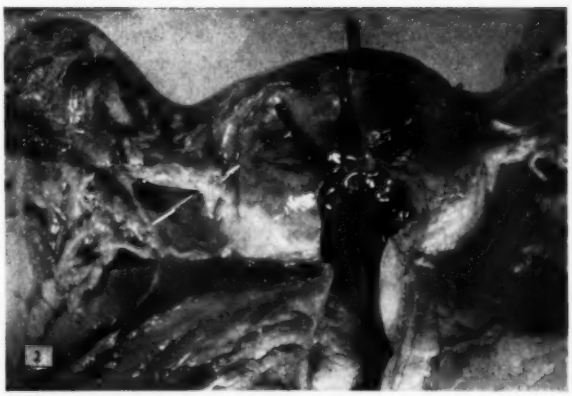
reddened and involved in the general peritoneal irritation. No perforated viscus was found. Inspection of the small pelvis showed the uterus to be normal but semifixed. Several drains were inserted, and the abdomen was closed.

The postoperative course was quite stormy with temperatures ranging between 101 and 103° F. The white cell count on the third postoperative day was 19,000. The fever was not influenced by any of the antibiotics, and the abdomen remained distended despite the use of a Wangensteen tube. The patient became irrational and comatose. Her temperature rose to 106° F., and she died on the fifth postoperative day, nine days after onset of the acute symptoms and eight months after the first complaint about a hemorrhagic discharge from the vagina.

Autopsy findings (only significant findings are given)—External description: The body measured approximately 165 cm. in length and weighed approximately 75 kg. The head and neck were not remarkable. The chest was symmetrically shaped. The abdomen was distended. Running parallel to and located to the right of the midline was a recently sutured surgical incision measuring about 6 cm. in length. Protruding from the right lower quad-





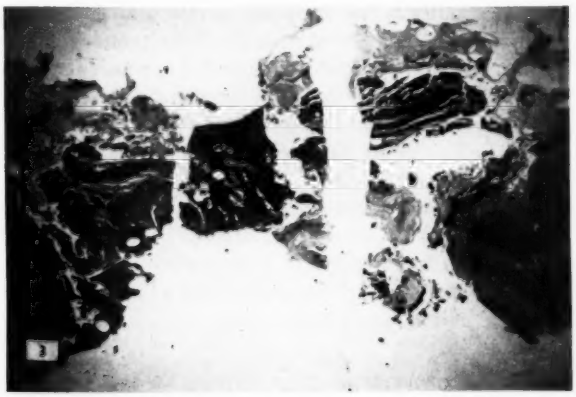


FIGURE 1 *(top)*. Picture of anterior wall of uterus, perforation in center partially covered with fibrin.

FIGURE 2 *(middle)*. Posterior view of uterus. The uterus is opened and a probe inserted which is seen to lead through the perforation. Note also the large amounts of fibrin, indicative of the severe peritonitis.

FIGURE 3 *(left)*. Photomicrograph of perforation tract in uterus, 35x magnification. The margins of the picture show myometrium. The center shows the perforation tract filled with necrotic debris. Note the absence of granulomatous inflammation of any tumor.

rant was a T tube. External genitals and extremities were not remarkable.

Internal description: The usual V-shaped incision was made. The peritoneum was dull and hyperemic. The small pelvis contained about 100 cc. of dirty pus and the intestines were plastered down in this region, obviously a picture of acute peritonitis. Examination of the intestines did not reveal any evidence of perforation. The organs of the small pelvis were covered by the intestines and could be visualized only after the adhesions of the small pelvis had been removed.

Organs of the small pelvis: The urinary bladder was covered with fibrin and was firmly adherent to the anterior wall of the uterus. The tubes and ovaries were enveloped in the inflammatory process in the small pelvis.

The uterus was removed with some difficulty from the posterior wall of the urinary bladder to which it was adherent by fibrinous adhesions. When this was accomplished, a perforation of the wall of the uterus which was located in the fundus and measured about 5 mm. in its greatest diameter could be seen. It had an irregular, ragged margin and was covered with fibrin (Figure 1). The uterus had been transformed into a thin-walled structure which was covered with greenish necrotic material and contained greenish purulent material. The cervical canal was extremely stenotic and could only be opened with great difficulty (Figure 2).

Microscopic report—The cervix was lined by well differentiated squamous epithelium. In the inferior region of the fundus the endometrium was low with small atrophic glands, and the myometrium here showed typical senile changes. In the remainder of the fundus and especially in the neighborhood of the perforation, the endometrium had disappeared and an ulcerated surface covered with fibrin and many segmented granulocytes could be seen. The inflammatory process extended for a great length. In the region of the perforation tract, the myometrium was also affected and a large area of complete necrosis was present. There was no evidence of a specific inflammatory process such as tuberculosis, nor were there signs of tumor formation (Figure 3).

Comment—From the clinical side, the case was interesting in again revealing the difficulty of finding the source of an acute peritonitis even with the abdomen open. In an elderly woman the appendix was suspected first and justifiably so. Since the main complaints were limited to the lower abdomen, stomach and gallbladder were ruled out. It has been our experience that with increasing frequency we find carcinoma of the large bowel responsible for such peritonitis. Inflammatory conditions of the internal genitals rarely are responsible for an acute generalized peritonitis. In this particular case, the source was hidden because the uterus was plastered down against the urinary bladder.

From a pathologic standpoint, the following explanation can be offered for the mechanism of the disease process: It is necessary to remember that the uterus is a hollow viscus which drains through the cervix. The channel in this case was almost completely occluded by extreme stenosis of the cervix, with subsequent accumulation of secretions and infection and perforation of the wall. While this particular sequence of events is rare, the condition of extreme cervical stenosis is not too uncommon. In elderly women it is usually produced by radiation rather than by any other agent. However, it also may occur more or less spontaneously.[1] Inflammatory conditions and extensive cauterization are sometimes responsible for such cervical stenoses. While these stenoses do not always lead to perforation, they frequently produce an inflammatory process with the formation of a pyometra. Such inflammatory process is usually limited to the region of its origin. However, we had an opportunity to perform an autopsy where such a pyometra was responsible for a generalized sepsis and death.

1. Kaufmann, Edward: Spezielle Pathologische Anatomie. Ed. 8. Berlin and Leipzig, Walter De Gruyter & Co., 1922, vol. 2, p. 1263.

CLINICAL STUDY

Ammonium and Potassium Cation Exchange Resin

IN TREATMENT OF CONGESTIVE HEART FAILURE

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A clinical evaluation of a potassium and ammonium resin was made on 8 patients with cardiac decompensation and edema. Six of the patients were able to tolerate higher sodium diets while taking resin than during their control period. MERCUHYDRIN® *effect was increased in most of the patients while they took resin.*

EVER since sodium restriction was found to be important in the control of cardiac failure and other edematous states, a material has been sought which might prevent absorption of sodium from the intestinal tract. In 1935 Adams and Holmes[1] found that phenolic resins were capable of ionic exchange actions. Dock,[2] in 1946, suggested the use of cation exchange resins in congestive failure to carry sodium out of the gastrointestinal tract. He noted the lack of toxicity of resin in dogs and the increase in fecal sodium during its administration. Several reviews of the literature on this subject have been published recently.[3,4] Most clinical trials of the acid forms of resins have been successful in decreasing sodium absorption from the intestinal tract.[5-7] The principal objection to the therapeutic use of resin has been the danger of producing severe metabolic acidosis and/or hypokalemia.[5-8] The resin employed in the present study has been modified in an attempt to overcome these objections and still retain considerable sodium-binding properties.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

This study was aided by grant to the University of Cincinnati College of Medicine from Smith, Kline and French Laboratories, who also supplied the resin used in this study.

RESODEC® is a cross-linked polyacrylic (polycarboxylic) cation exchange resin in which acid H+ ions have been replaced by NH_4+ and K+ ions. Each 15 gm. of resin contains 50 mEq. (902 mg.) of ammonium ion and 20 mEq. (782 mg.) of potassium. In experimental work[9] with this resin it was noted that in the acid medium of the stomach the resin gave up its cations to solution. As the chyme approached neutrality it exhibited a slight affinity for binding cations. At *p*H 7.5 the resin exhibited its maximum effect. Therefore the maximum binding effect of this resin takes place in the upper small bowel after some absorption of food has already taken place. Iron, copper, cobalt, magnesium and manganese are not appreciably bound by this resin in vivo. Although calcium is bound in vitro, balance studies have shown that it is not bound in vivo.[10] In vitro this resin has been found to bind 5.9 mEq. of sodium per gram at *p*H 8. Balance studies in humans showed the resin was capable of binding from 1 to 4 mEq. of sodium per gram. The lower sodium-binding power of the resin was found in patients with severe cardiac diseases. In this study,

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the resin was administered to patients hospitalized for chronic congestive failure to determine its value in control of edema and whether or not serious disturbances in blood chemistries would occur.

Methods

Eight patients with congestive heart failure were chosen for study from patients admitted to the wards of Brown Veterans Administration Hospital. These patients had been treated initially by the usual methods without the use of exchange resins; we attempted to select patients whose edema tended to recur unless mercurial diuretics were given. All patients were men, ranging from 54 to 66 years of age. Four had rheumatic heart disease, 3 had arteriosclerotic heart disease and 1 had hypertensive heart disease. All patients were observed during the study on a single ward, under direct supervision of at least one of us. The nature of the study was explained fully to all patients at the onset and none was accepted unless he expressed willingness to cooperate. Patients were allowed to be up and about the ward if their clinical conditions permitted.

After digitalis dosage was adjusted to the optimum level, sodium content of the diet was varied to determine the level at which weight gain occurred. Diets containing 300 to 1200 mg. of sodium per day were specially prepared by the dietetic service; sodium values were determined from the Mead Johnson tables[11] and correction was made for uneaten portions. Sodium content of 1200 to 2800 mg. per day was obtained by issuance of weighed amounts of salt each day to be added by the patient to the basic 1200 mg. of sodium diet. Values of sodium intake up to 3600 mg. were obtained by giving uncoated salt tablets. Patients were weighed on the same clinical beam balance each morning after voiding and before breakfast, wearing standard hospital coats and trousers. Changes in clinical condition corresponded quite closely to variations in weight.

Fasting levels of serum sodium, potassium, calcium, carbon dioxide-combining power, chloride and blood urea nitrogen were determined at weekly intervals. Sodium determinations were made by the method of Butler and Tuthill,[12] potassium by the method of Kramer and Tisdall,[13] calcium by the method of Clark and Collip,[14] and chloride by the method of Whitehorn.[15] Carbon dioxide-combining power was determined by the method of Van Slyke and Cullen.[16] Urea nitrogen was measured on the sodium tungstate filtrate by the Karr method.[17] Sodium and chloride content of 24 hour urine samples was determined twice weekly. Complete blood counts and routine urinalyses were done each week, and a chest film and a 12 lead electrocardiogram were made every two weeks.

The cation exchange resin was supplied in packages containing 15 gm. of mixed ammonium and potassium salt. The resin was added to standard or low sodium milk (LONALAC®) and taken with meals. Ammonium chloride and mercurial diuretics were given as needed to control the failure or to estimate the "dry" weights of the patients.

Separate mercuhydrin tests were done to compare the response in the control periods and during resin therapy. After a constant weight was achieved, each patient was given 2 cc. of

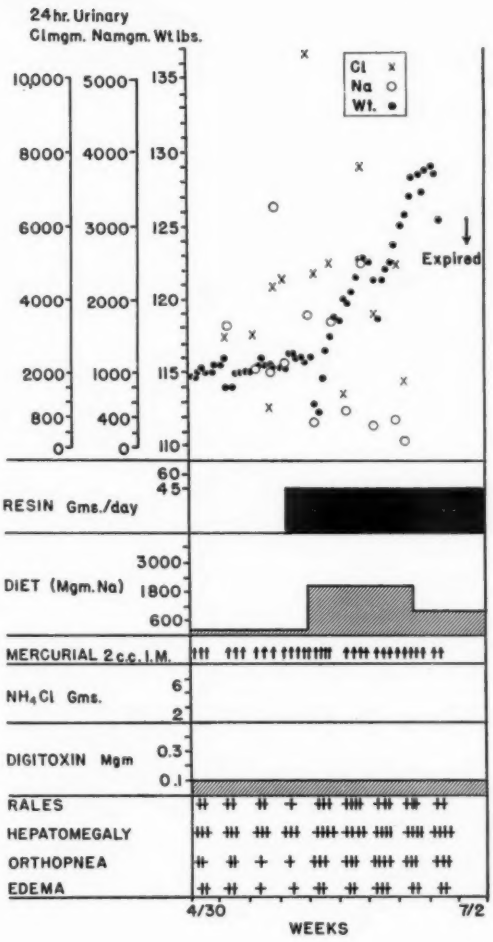

FIGURE 1 *(Case 1)*. A 55 year old white man with rheumatic heart disease was admitted to the hospital March 5, 1950. He was seriously ill and had multiple pulmonary infarctions. With 300 mg. of sodium intake in addition to resin, the patient improved and lost weight. A sodium intake of 2000 mg. plus resin produced an increase of 13 pounds in four weeks. Reduction of the sodium intake to 1200 mg. per day plus resin was followed by a weight loss of 3½ pounds in four days before the patient died as a result of a mesenteric thrombosis.

Postmortem examination revealed moderate bilateral hydrothorax, an adherent thrombus in one of the major branches of the lower lobe of the left lung and multiple areas of pulmonary infarction as well as pulmonary congestion. The heart weighed 550 gm. There was dilatation of the right auricle and ventricle, and right ventricular hypertrophy. The left auricle was dilated and showed mural thrombus formation. The tricuspid valve showed slight thickening and fibrosis with puckering of the cusps. The mitral valve was markedly stenosed and the aortic valve showed thickening of the cusps but was functionally patent. The liver weighed 1300 gm. and the spleen weighed 250 gm. Both organs showed chronic passive congestion. The kidneys revealed moderate arterial thickening and fecal scarring. Bowman's space was enlarged and filled with fibrin. The distal two feet of terminal ileum showed a well demarcated area of dark hemorrhagic congestion and edema of the bowel which was attributed to a mesenteric thrombosis. A similar area was seen in the transverse and descending colon. The remainder of the large and the small bowel was normal except for moderate passive congestion.

mercuhydrin intramuscularly on two successive days. Note was made when the patient's weight returned to its original level. At this time the mercuhydrin test was repeated. If the initial test was performed during the control period, the second test was made while the patient was taking resin, or vice versa.

Results

The 8 patients with cardiac failure were studied for a total period of 826 days. It was deemed necessary to have a rather long control period of preliminary observation to establish the clinical course without resin therapy. The combined control period was 280 days of direct observation by the authors. Treatment periods varied from 9 to 36 days. Two of our patients (Cases 3 and 4) received two separate courses of resin without alteration of other factors. Another patient (Case 5) received two courses with an increase in resin administration to 60 gm. per day during one. Adequate control periods for weight stabilization intervened between courses of resin. In addition to these courses of resin, 5 patients were given resin in conjunction with special trials of mercuhydrin injections.

Of the 8 patients, all but 2 showed a decrease in weight and improvement in signs of

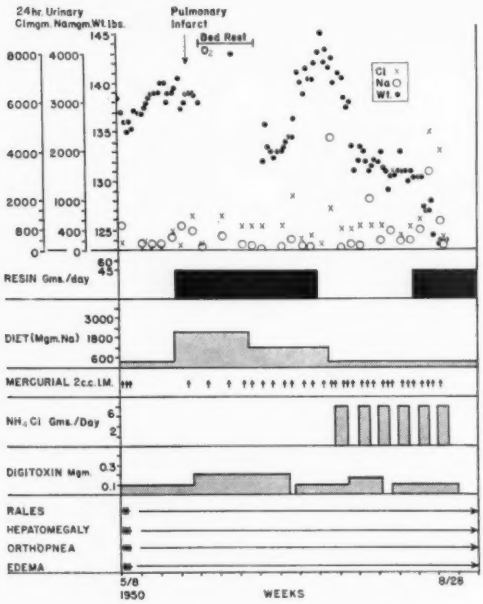

FIGURE 2 *(Case 2)*. A 59 year old white man with rheumatic heart disease was admitted March 20, 1950. The patient was seriously ill and had multiple pulmonary infarctions. The patient's response to resin was not good while he was receiving the resin and a high sodium intake. A 300 mg. sodium intake in addition to resin resulted in improvement and a loss of 7½ pounds in two weeks. The patient died shortly after the study.

Postmortem examination revealed moderate bilateral hydrothorax, pulmonary congestion and multiple pulmonary infarcts. The heart weighed 560 gm. There was marked dilatation and hypertrophy of the right ventricle. The tricuspid valve was slightly thickened, and there was a moderate amount of antemortem thrombus attached to the wall of the left auricle. The mitral valve was markedly thickened and distorted, and calcific plaques were present in both leaflets of this stenotic valve. The aortic valves were thickened but pliable. The liver weighed 1300 gm. and the spleen weighed 320 gm. Both organs showed chronic passive congestion. Both kidneys evidenced moderate arterionephrosclerosis with a few retention cysts. The small and the large bowel showed passive congestion with occasional areas of submucosal hemorrhage. No ulcerations or other lesions were noted.

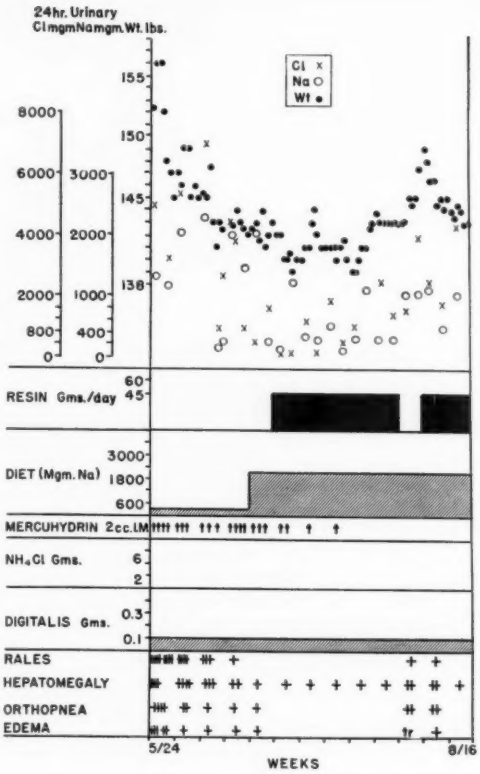

FIGURE 3 *(Case 3)*. A 50 year old white man who had hypertensive cardiovascular disease and arteriosclerotic heart disease was admitted September 27, 1949. The patient was maintained edema-free with resin plus 2000 mg. sodium daily. The edema recurred when the resin was discontinued; he remained free of edema on an outpatient trial of the resin.

failure while taking resin (Figures 1 to 8). One of these 2 (Figure 6, Case 6) lost no weight but responded well to the mercuhydrin test. The other patient (Figure 1, Case 1) had such poor cardiac reserve that he was in severe failure on a 300 mg. of sodium diet. When sodium intake was increased to 2000 mg. per day plus resin, he rapidly gained 13 pounds of weight. Resin was continued and sodium intake was reduced to 1600 mg. per day; the patient lost 3½ pounds in six days before expiring of mesenteric thrombosis. The 6 other patients lost from 1 to 7½ pounds of weight while taking resin. Average weight loss per trial was 4.2 pounds. Two patients (Cases 1 and 2) had severe failure at bed rest. Both these patients also had multiple pulmonary infarctions during their hospital stay and fairly marked renal disease.

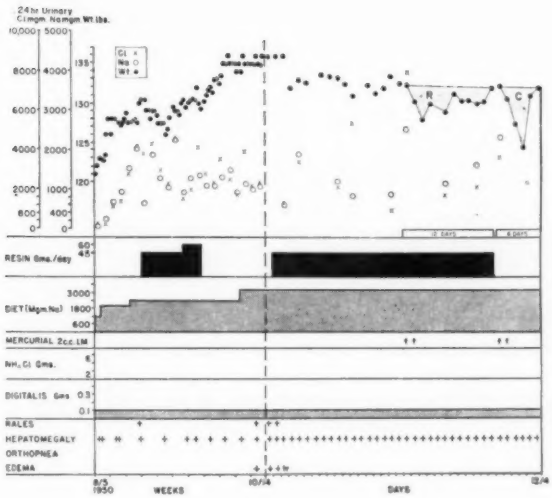

FIGURE 4 *(Case 4)*. A 59 year old white man who had arteriosclerotic heart disease was admitted June 15, 1950. When given 2000 mg. sodium per day plus resin, the patient's weight remained stable. He gained 7 pounds after the resin was discontinued. With a sodium intake of 2000 mg. plus resin, the patient's condition improved. The shaded areas show the accentuation of the mercuhydrin diuretic effect by the resin. The shaded area R (resin) represents 145 per cent of C (control).

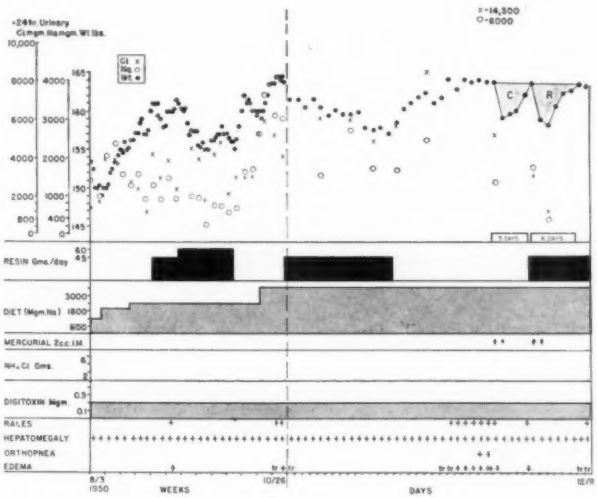

FIGURE 5 *(Case 5)*. A 56 year old white man with rheumatic heart disease was admitted July 6, 1950. On a regimen of 2400 mg. sodium plus 45 gm. of resin, the patient showed no improvement. When the resin dosage was increased to 60 gm., the patient lost 5½ pounds in 26 days. With a 3600 mg. sodium intake plus 45 gm. of resin, the patient improved and lost 7½ pounds in 15 days. The mercuhydrin trials showed no difference. R (resin) was 102 per cent of C (control).

The patients' weights did not necessarily follow a smooth downward curve during the resin trials. It was found that often during the first few days of resin therapy there was marked diuresis and weight loss (Figures 3, 4 and 8). Following this initial diuresis, the patients' weights either decreased slowly or increased, depending on the ultimate benefit each patient received from the resin. This diuresis usually occurred on the third day of resin administration and the average weight loss observed was 3½ pounds. This phenomenon was observed in 9 of 12 trials of resin.

Three of our patients received mercuhydrin injections during their control periods (Figures 1, 2 and 3). Reduction of mercuhydrin during therapy was effected only in Case 3. In this patient, injections were gradually reduced from

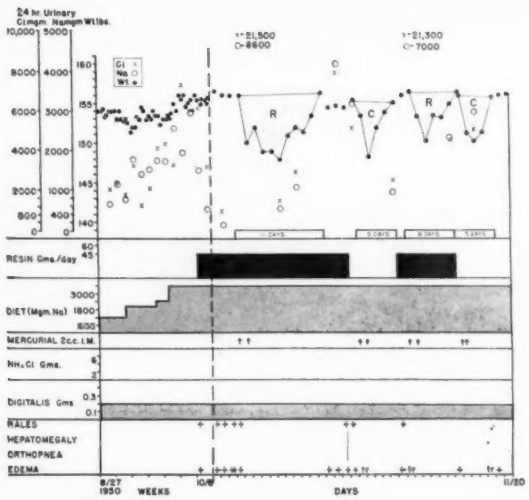

FIGURE 6 *(Case 6)*. A 59 year old white man with arteriosclerotic heart disease was admitted August 24, 1950. With a 3600 mg. sodium intake plus resin, the patient showed no response in nine days. The first mercuhydrin trial showed that the effect of the mercuhydrin was markedly accentuated by the resin. R (resin) was 345 per cent of C (control). In the second mercuhydrin test, the effect of the mercuhydrin was only slightly increased by the resin. The R (resin) was 112 per cent of C (control).

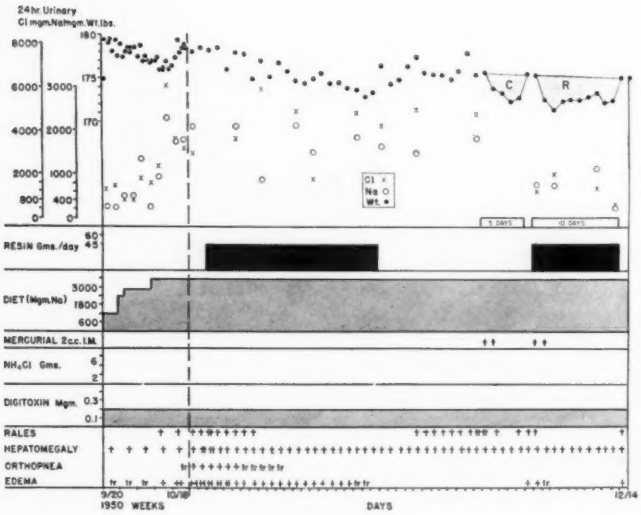

FIGURE 7 *(Case 7)*. A 66 year old white man with hypertensive cardiovascular disease was admitted August 28, 1950. On a daily regimen of 3600 mg. of sodium plus resin, the patient improved and lost 5 pounds in 20 days. The effect of mercuhydrin was accentuated by concomitant administration of resin. R (resin) was 251 per cent of C (control).

four to none a week over a period of four weeks. This patient weighed one pound less at the end of the resin trial than during his control period. All other factors were unaltered. This patient was discharged to his home with one month's supply of resin. He failed to return for his follow-up examination but on a subsequent admission stated that he had remained edema-free until his resin supply was exhausted. In the hospital this patient was on a 2000 mg. of sodium diet and was on an unrestricted diet at home.

In 5 patients the response to mercuhydrin in resin trial and in control periods was compared. In evaluating the benefit the patient received from each resin trial, it was felt that neither the lowest weight observed nor the number of days until the weight returned to the original level

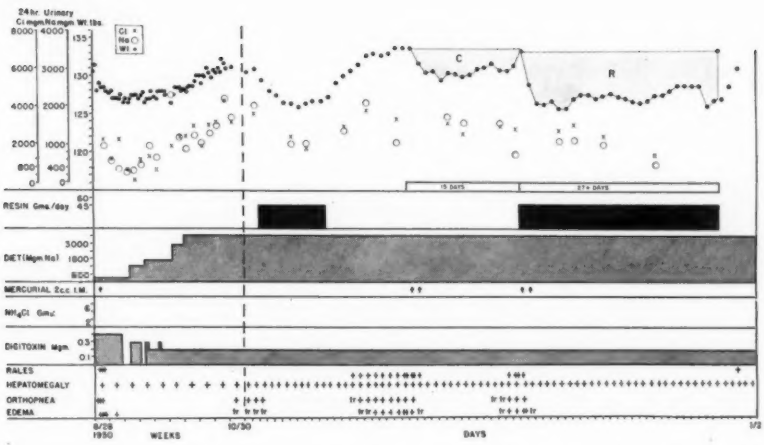

FIGURE 8 *(Case 8).* A 56 year old white man with rheumatic heart disease was admitted August 14, 1950. When receiving 3600 mg. of sodium plus resin daily, the patient improved and lost 4 pounds in nine days. The effect of the mercuhydrin was markedly increased by the resin. The patient's weight did not return to the previous level until the administration of resin was discontinued. R (resin) was in excess of 259 per cent of C (control).

would best represent the amount of edema absent or the benefit the patient derived from each test. As seen in the shaded areas of Figures 4, 5, 6, 7 and 8, the weight at the beginning and end of each test was used as a base line. The daily weights between these periods were used as the other borders of an area which was computed in each instance. When the shaded areas for resin trial and control periods were compared on the graphs, it was found that in five of the six trials the effect of mercuhydrin was accentuated by concomitant administration of resin. In the other instance it was approximately equal. Figure 8 shows that the patient's weight failed to reach the original level while he was taking resin. After resin was discontinued, the patient's weight rapidly rose to its original level.

Blood chemistries during the periods of resin administration showed no significant differences from those during the control periods in any of our patients. These data are not presented in detail since no change was noted.

Sodium content of 24 hour urine specimens generally tended to be lower while the patients were taking resin.

The only side effect noted was mild to moderate constipation in 3 patients. None of the patients objected to taking the resin.

Discussion

Some favorable therapeutic effect from resin administration was noted in all our patients. As might be suspected from previous sodium-binding studies made on this resin, the patients with severe congestive heart failure (Figures 1 and 2) did not respond as well as did the patients who merely had the problem of edema which recurred unless sodium intake was rigidly restricted. In this series, it was found that the patients with milder failure could be kept comfortable and edema-free while taking diets containing a fairly liberal amount of sodium. In our only outpatient trial after hospitalization this was borne out. The patient who was able to discontinue mercuhydrin injections was also in the group with milder failure. The other 2 patients who showed no reduction in the need for mercuhydrin during the therapy had the severest type of failure on bed rest as well as multiple pulmonary infarctions during their courses (Figures 1 and 2). It was felt, however, that the favorable response in these 2 patients while taking resin plus a 300 mg. sodium diet warranted future trials with resin in conjunction with a lower sodium diet for the patient with very severe cardiac failure.

An early diuretic effect was seen rather consistently in our patients. This effect has not been described with the use of acid resins. However, this phenomenon had been previously observed in patients treated with the ammonium form of exchange resin by Kraus.[18] We felt, as he did, that the diuretic effect was produced by absorption into the body of an ammonium salt which acted similarly to ammonium chloride.

There is some evidence in the literature and in our series that mercuhydrin injections could be reduced or eliminated by the use of resin. It was felt that a more direct evaluation of the comparison of mercuhydrin with and without resin could be effected. The method described before was devised. The results of this semiquantitative evaluation showed that mercuhydrin injections usually gave better results when combined with resin therapy.

Since hypokalemia and metabolic acidosis have been frequently observed with clinical use of acid resins, one of our principal objectives was to determine whether it was safe to use the resin. No disturbance was noted in the blood chemistries of any of our patients. This was of increased significance in Cases 1 and 2, since both of these patients were found to have moderate arterionephrosclerosis at postmortem examination. Renal disease has been described as a contraindication to resin therapy because the danger of acidosis is enhanced under these conditions. We do not wish to imply, on the basis of these 2 cases, that this medication should be used indiscriminately in the face of marked renal disease. We present them merely to demonstrate an increased margin of safety.

Some previous studies on various forms of resins have shown much more marked weight loss and loss of edema during the resin therapy. The less dramatic results in this series are thought to be due to several factors: (1) The prolonged period of control eliminated any improvement due to factors other than resin administration, and (2) all patients had severe enough failure to justify admission to a Veterans Administration Hospital.

The scope of this paper was to describe a small series of intensively studied, hospitalized patients. However, cation exchange substances might offer more in the treatment of the ambulatory cardiac patient with more easily controllable failure than in the treatment of the hospital patient. Since there were no disturbances in the acid-base balance and encouraging therapeutic results were seen in the present series of patients during resin administration, it is felt that extensive trials of resin ought to be made on ambulatory patients.

REFERENCES

1. Adams, B. A. and Holmes, E. L.: Absorptive properties of synthetic resins. I. J. Soc. Chem. Ind. 54:1T, 1935.
2. Dock, W.: Sodium depletion as a therapeutic procedure: The value of ion exchange resins in withdrawing sodium from the body. Tr. A. Am. Physicians 59:282, 1946.
3. Dock, W. and Frank, R.: Cation exchangers: Their uses and hazards as aids in managing edema. Am. Heart J. 40:638, 1950.
4. McChesney, E. W., Dock, W. and Tainter, M. L.: Ion exchange resins in edema. Medicine 30:183, 1951.
5. Irwin, L., Berger, E. Y., Rosenberg, B. and Jackenthal, R.: The effect of a cation exchange resin on electrolyte balance and its use in edematous states. J. Clin. Investigation 28:1403, 1949.
6. Danowski, T. S., Greenman, L., Mateer, F., Peters, J. H., Weigand, F. A., Mermelstein, H. and Clarke, C. E.: Carboxylic cation exchange resin studies in animals and humans. J. Clin. Investigation 29:807, 1950.
7. Kahn, S. S. and Emerson, K., Jr.: Experiences with the use of cation exchange resins in the treatment of edema. J. Clin. Investigation 29:827, 1950.
8. Martz, B. L., Kohlstaedt, K. G. and Helmer, O. M.: Use of ion exchange resins in the management of congestive heart failure and cirrhosis of the liver. J. Lab. & Clin. Med. 36:962, 1950.
9. Heming, A. E. and Flanagan, T. L.: Site of action of cation exchange resins in removal of sodium from the G. I. tract. Federation Proc. 10:307, 1951.
10. Flanagan, T. L., Sax, M. F. and Heming, A. E.: Toxicity studies on amberlite XE96, a carboxylic-type cation exchange resin. To be published.
11. Bills, C. E., McDonald, F. G., Niedermeier, W. and Schwartz, M. C.: Sodium and potassium in foods and waters. Determination by the flame photometer. J. Am. Dietet. A. 25:304, 1949.
12. Butler, A. M. and Tuthill, E.: An application of the uranyl zinc acetate method for determination of sodium in biological material. J. Biol. Chem. 93:171, 1931.
13. Kramer, B. and Tisdall, F. F.: A clinical method for the quantitative determination of potassium in small amounts of serum. J. Biol. Chem. 46:339, 1921.
14. Clark, E. P. and Collip, J. B.: A study of the Tisdall method for the determination of blood serum calcium with a suggested modification. J. Biol. Chem. 63:461, 1925.
15. Whitehorn, J. C.: A system of blood analysis. Supplement II. Simplified method for the determination of chlorides in blood or plasma. J. Biol. Chem. 45:449, 1921.
16. Van Slyke, D. D. and Cullen, G. E.: In Levinson, S. A. and MacFate, R. P.: Clinical Laboratory Diagnosis. Ed. 3. Philadelphia, Lea & Febiger, 1946, pp. 234-239.
17. Karr, W. G.: A method for the determination of blood urea nitrogen. J. Lab. & Clin. Med. 9:329, 1924.
18. Kraus, H.: The use of a cation exchange resin in patients with cardiac edema. J. Clin. Investigation 29:829, 1950.

SCIENTIFIC EXHIBIT

The Diagnosis of Thyroid Disease

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THE diagnosis of thyroid disease is performed by two sets of examiners—the physician and the laboratory technician. Of the two, the physician is the more important; unfortunately more homage is generally paid to the laboratory technician and his figures. These charts show in schematic fashion the functions measured in the laboratory and some of the ways in which these functions may seem to be disturbed and lead to contradictory results.

The initial three figures explain the three principal tests used to diagnose thyroid disease and indicate the symbols to be used in the remaining nine figures. The next three figures illustrate the results of these tests in the usual situations of normal, hypothyroid and hyperthyroid individuals. The final six figures show situations where one or more of the tests do not correlate with the true clinical state.

The authors wish to acknowledge the aid of
the artist, Miss Elizabeth Van Rensselaer.

PROTEIN-BOUND IODINE

A Test for the Blood Level of Thyroid Hormone

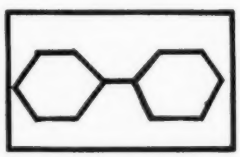
INCREASED BY:

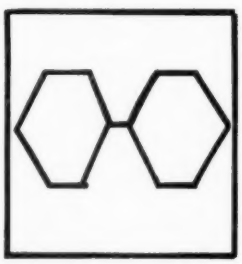
1. Hyperthyroidism.
2. Artifacts, e.g., ingestion of large amounts of iodine—particularly organic iodine.
3. Physiologic increase in thyroid function as in pregnancy.

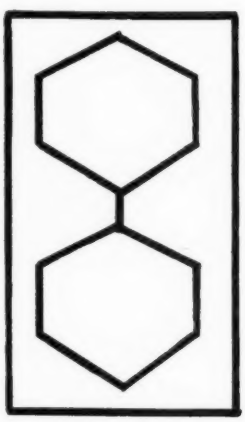
DECREASED BY:

1. Hypothyroidism.
2. Certain hypoalbuminemic states.
3. Artifacts with certain types of assay, e.g., mercurial diuretics in the Chaney technic.

SUBNORMAL	NORMAL	SUPERNORMAL
Below 4 mcg. per cent	4 to 7.5 mcg. per cent	Above 7.5 mcg. per cent







SERIAL DETERMINATIONS ARE OF MORE VALUE THAN SINGLE

FIGURE 1

BASAL METABOLIC RATE

A Test to Compare Oxygen Consumption at Rest with a Set of "Normal" Standards

INCREASED BY:

1. Nervousness.
2. Any state associated with increased oxygen consumption, e.g., leukemia, pheochromocytoma.
3. Improper definition of normal oxygen consumption.
4. Technical artifacts.
5. Excess thyroid hormone.

DECREASED BY:

1. Deficiency of metabolic stimulus from pituitary, adrenal, etc.
2. Improper definition of normal oxygen consumption, e.g., extreme obesity.
3. Technical artifacts.
4. Deficiency of thyroid hormone.

SUBNORMAL	NORMAL	SUPERNORMAL
Below −20 per cent	−20 to +20 per cent	Above +20 per cent

SERIAL BASAL METABOLIC RATES ARE OF CONSIDERABLE USEFULNESS;
SINGLE BASAL METABOLIC RATES ARE OFTEN DECEIVING

FIGURE 2

RADIOIODINE UPTAKE TEST

A Test of Thyroid-Epithelial Hyperplasia

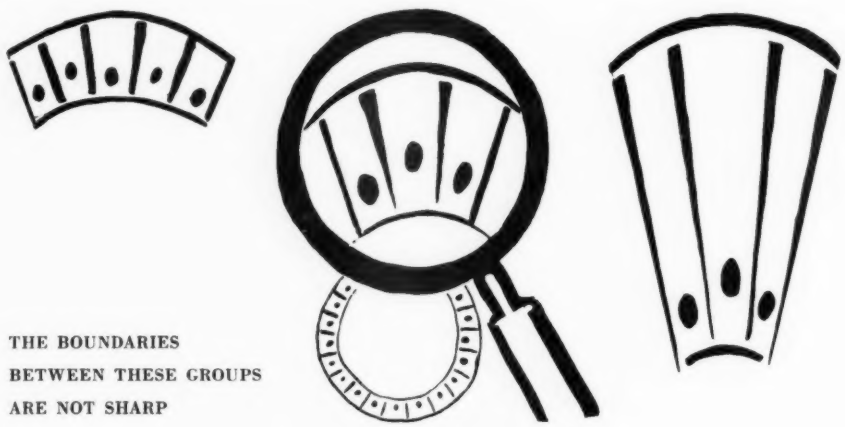
INCREASED BY:

1. Thyroid-stimulating hormone (TSH).
2. Antithyroid drugs which enhance the endogenous production of TSH.
3. Iodine starvation.

DECREASED BY:

1. Iodine (dilution of radioiodine combined with induced involution of the thyroid).
2. Antithyroid drugs (blocking action while drug is being taken).
3. Exogenous thyroid extract (induced involution of thyroid by suppression of TSH production).
4. Inflammatory processes (thyroiditis).

SUBNORMAL	NORMAL	SUPERNORMAL
Below 15 per cent	15 to 35 per cent	Above 35 per cent



THE BOUNDARIES BETWEEN THESE GROUPS ARE NOT SHARP

FIGURE 3

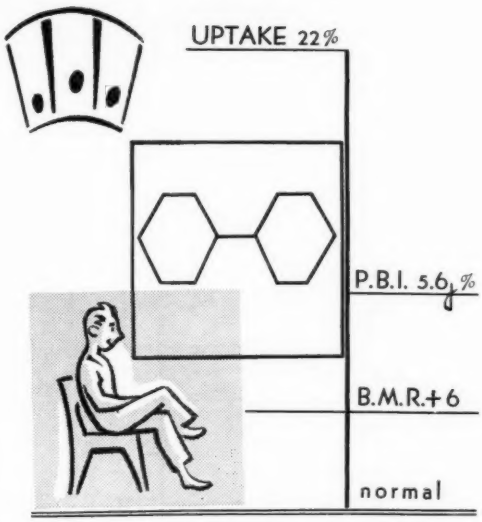


FIGURE 4

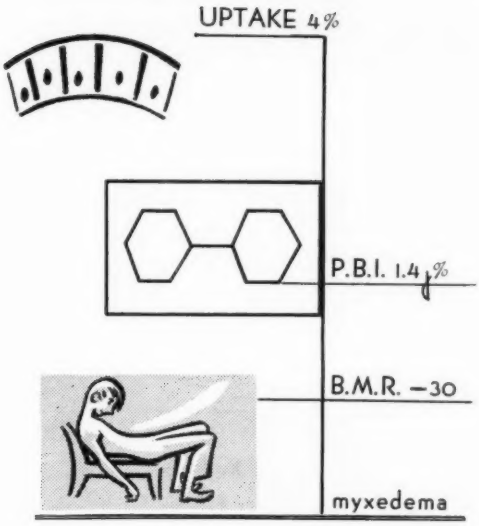


FIGURE 5

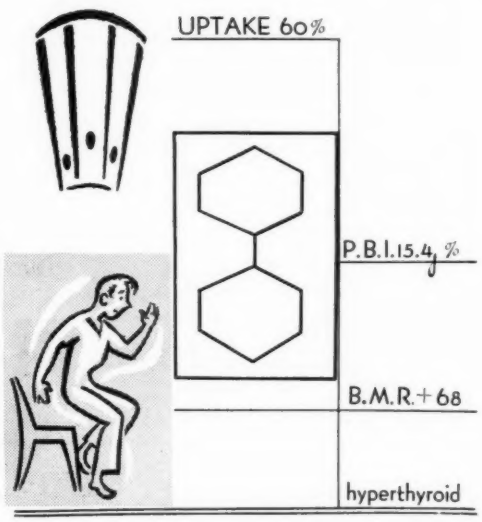


FIGURE 6

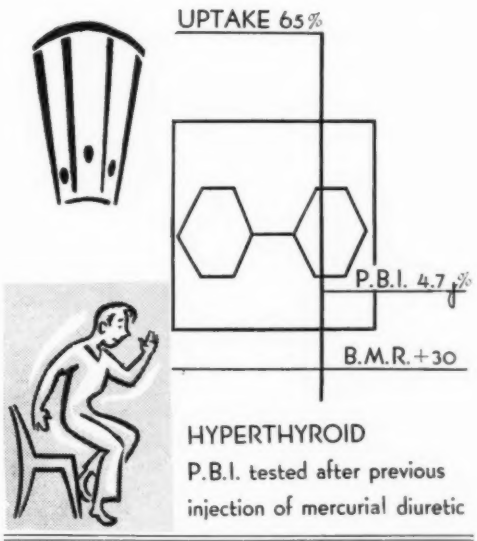


FIGURE 7 *(right)*. A patient with hyperthyroidism plus heart failure who has been receiving daily injections of a mercurial diuretic. Note the high oxygen consumption and high uptake of I^{131} by the thyroid coupled with a normal protein-bound iodine level. Certain technics for performing blood iodine assays give falsely low values in the presence of mercury.

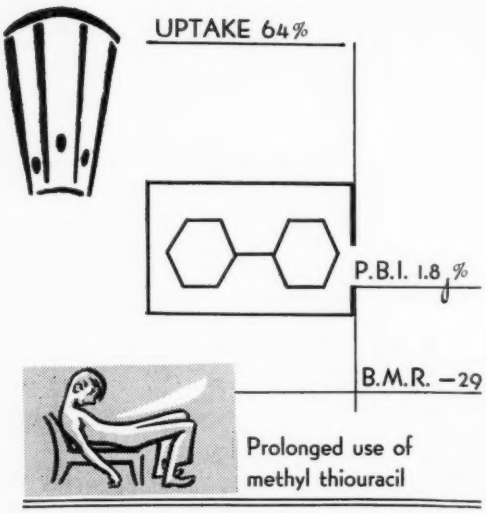


FIGURE 8. Results of the three basic tests when done on a patient rendered myxedematous by methyl thiouracil; the tests were done seven days after the antithyroid drug was stopped. The low level of protein-bound iodine and oxygen consumption fit with the clinical status; the abnormally high level of radioactive iodine indicates the degree of hyperplasia present in the thyroid follicles and in this situation is at complete variance with the clinical condition.

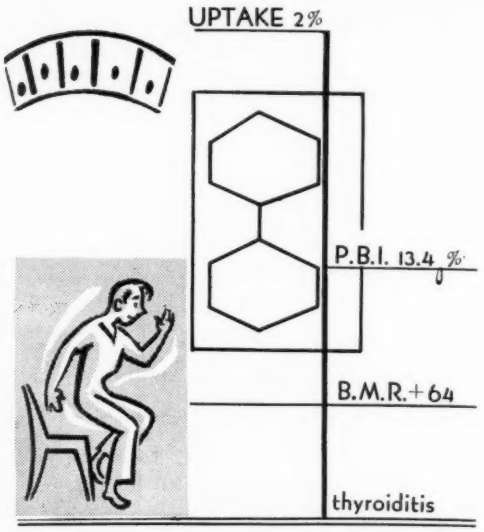


FIGURE 9. Results of the tests done on an elderly woman who was clinically severely "toxic" with hyperthyroidism. The increased oxygen consumption and the elevated level of blood iodine support the clinical impression—the extremely low level of iodine uptake does not. An eventual thyroidectomy revealed thyroiditis.

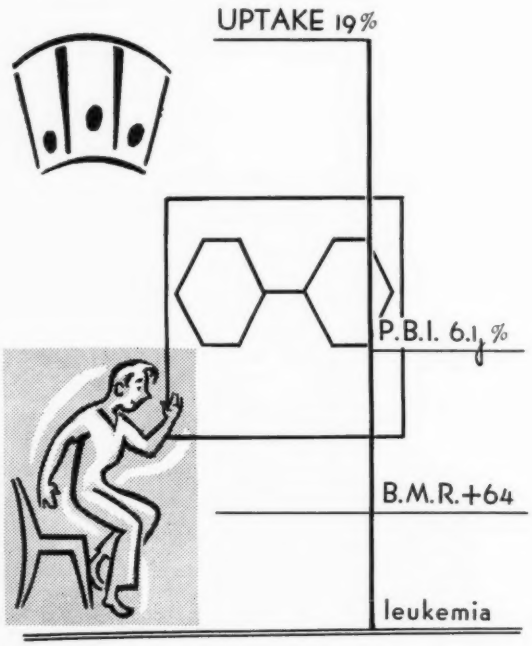


FIGURE 10. One of the classic examples of increased oxygen consumption in the absence of thyroid disease—leukemia. The normal uptake of radioactive iodine indicates here the true picture of thyroid function.

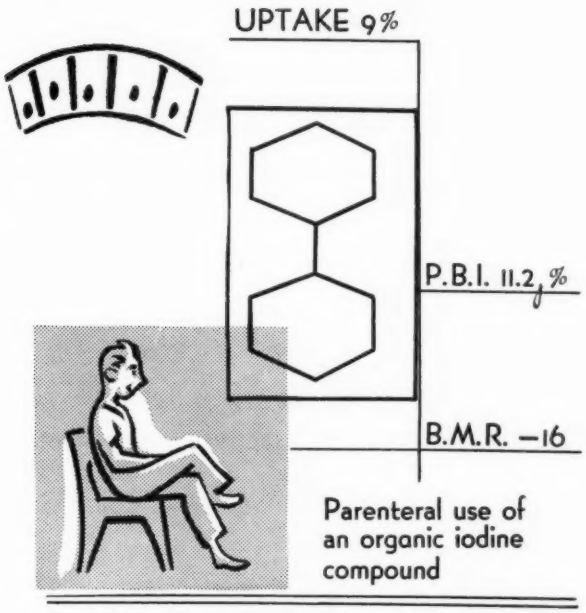


FIGURE 11. This represents a nervous patient who had a protein-bound iodine determination performed 60 days after a cholecystogram. The low-normal basal metabolic rate and somewhat low uptake of radioactive iodine reveal the true state of affairs. The low uptake of iodine is probably the result of dilution of radioactive iodine with excessive quantities of stable iodine plus involution of the thyroid induced by the iodine given at the time of the cholecystogram.

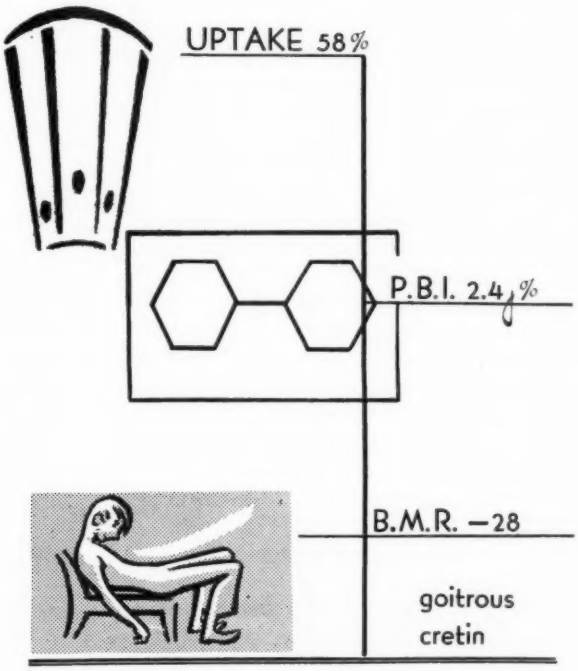


FIGURE 12. This is an interesting situation with a goitrous cretin; the low oxygen consumption and the low level of circulating thyroid hormone agree with the clinical state. The high uptake of radioactive iodine indicates the degree of follicular hyperplasia present in the goiter—a hyperplasia not associated with effective overfunction of the thyroid.

GENERAL PRACTICE *Review*

This department offers the latest, proved methods for the treatment and management of commonly encountered conditions based on the extensive experience of the physicians who prepare these summaries especially for POSTGRADUATE MEDICINE.

The Use and Abuse of Ointments in Eye Diseases

SAMUEL J. MEYER AND SAMUEL SCHALL

Chicago, Illinois

MANY of the medications used in ophthalmic practice are now available as eye ointments. In the use of these ointments it is essential to understand both the pharmacology of the drug in the ointment vehicle and the nature of the eye disease to be treated. There are several rules to follow in the use of ophthalmic medicated ointments. Those most commonly used will be discussed, as well as some of the misconceptions or abuses of some ointments.

Use of an ointment vehicle is indicated principally when it is desirable for the medication to remain on the skin or in the conjunctival sac for prolonged effect. The drug included in the ointment therapy has a better chance to produce an effect rather than to be lost through tears over the lid margins or down the lacrimal passages. Atropine ointment is used effectively, for instance, for cycloplegic refraction in children. At the same time, any systemic effect from absorption through the lacrimal passages is avoided.

Swan[1] has shown that in some instances the use of an ointment base for therapy is actually superior and preferable to another vehicle. According to him the penetration of drugs into the cornea, for example, is dependent on the relative physical properties of the drug and the vehicle. A drug should be given in a vehicle for which it has less affinity than for the cornea and conjunctival epithelium. This means that highly water-soluble drugs should be used in an oil or ointment vehicle while oil-soluble drugs should be used in an aqueous or AQUAPHOR® vehicle. Thus, water-soluble penicillin salts, for example, are more effectively absorbed through the intact corneal epithelium when administered in an anhydrous petrolatum base. On the other hand, aqueous drops, methyl cellulose or aquaphor vehicle theoretically should be used for the oil-soluble steroid, cortisone.

The base used for most eye ointments is soft white petrolatum. In some cases this is mixed in a ratio of 3 to 1 with anhydrous lanolin. When water-soluble drugs are incorporated in the ointment, they are dissolved in sterile water and then mixed with the anhydrous lanolin which picks up the solutions readily. Since most eye ointments contain no preservative, sterile technic in packaging is essential.[2]

When eye ointments are used only occasionally, the contents or the caps of the tubes

may become contaminated. It is necessary to observe some precautions in the use of the ointment. To minimize the chance for contamination, one may (1) immerse the ointment tube in a solution of ZEPHIRAN® 1:1000 to 1:3000 for three minutes, (2) wipe the cap and neck of the tube with alcohol or (3) discard the first ¼ to ½ inch of the ointment before instilling it into the conjunctival sac.

The easiest method of administering an eye ointment is to retract the lower lid and instill the ointment from a collapsible tube into the lower fornix. If the tube is warmed by the heat of the hand the ointment will flow more easily. A mistake often made is that the doctor fails to instruct the patient exactly how to instill the ointment into the lower fornix. Consequently in many cases the patient applies the ointment to the outer surface of the lids and not *into* the cul-de-sac for which it is intended. With atropine or penicillin ointment, for instance, instead of a therapeutic effect a sensitization to the drug may result.

Another error in the use of an ointment may be the doctor's overlooking the fact that a working person must have clear vision, which is blurred by such medication. The patient must be interrogated about his work and, where indicated, aqueous, oily or 1 per cent methyl cellulose vehicle must be substituted. In these cases the ointment may be prescribed for use before retiring.

Under certain conditions, ointments are contraindicated. One of these is in the period immediately following a cataract operation. It has been shown that ointments can pass through the open wound and can be found in the anterior chamber of the eye.[3] An ointment is also contraindicated in plastic procedures around the lids where maceration of the skin graft may occur. A third contraindication is in inflammatory skin lesions around the lids that may be moist, open or weeping.

Finally, ointments have been shown to inhibit healing of corneal wounds (with or without antibiotics present). In the case of local anesthetics, however, ointments are less inhibitory to corneal healing than are solutions.[4] In clinical practice the latter objections to ointments are not readily apparent.

It is beyond the scope of this paper to give a comprehensive review of ocular therapeutics or pharmacology of the drugs used. For this, the reader is referred to other sources.[5-7] However, a short summary of frequent ocular conditions and their therapy with ointments is indicated. Treatment of various ocular lesions and some of the common ophthalmic ointments used for their therapeutic effect are as follows:

The Lids

1. *Blepharitis*—The inflamed, reddened, crusted or ulcerated lid margins may be treated by means of 10 per cent sodium SULAMYD® ointment or an appropriate antibiotic three times a day. This is effective in the chronic staphylococcic or Morax-Axenfeld type of blepharitis. The effect of the ointment is enhanced if the patient takes some care in using hot compresses and in mechanically removing the scales before applying the ointment. The margins of the lids are then treated with a small amount of ointment spread on a cotton-tipped toothpick.

For the nonulcerative seborrheic type of blepharitis a 5 per cent ointment of sodium proprionate has been found effective. A 0.5 to 1 per cent sulfur ointment applied locally, along with the treatment of any associated scalp lesions, has also been recommended. A course of seven daily treatments may be prescribed followed by two or three days of treatment every second or third week.

2. *Styes*, which consist of acute pyogenic infections of the sweat glands in the lid called hordeola, or of a deeper sebaceous meibomian gland called chalazions, may be treated locally with a suitable antibiotic ointment. If the local lesion is not aborted, the conjunctival sac at least is kept relatively clean, preventing a severe conjunctivitis.

Sulamyd or terramycin ointment may be used with some benefit in these cases before and after surgical intervention.

3. *Contact dermatitis* of the lids usually is caused by sensitivity to the common offenders —eyelash makeup, nail polish, or cosmetics containing orris root—and can best be treated by avoiding the sensitizing agent. Topical ap-

plication of PYRIBENZAMINE® ointment, aluminum subacetate (hydrosol ointment) or ointment of 10 per cent naftalin will relieve the itching and severe redness. In cases where there is profuse moisture or weeping, however, it is a mistake to use ointments. In this stage, compresses are indicated until the lesions are no longer moist. Following this a bland 2 per cent zinc oxide ointment may be used on the skin. Soap and water should be avoided until the dermatitis is healed, using, if necessary, a bland cold cream or vanishing cream for cleansing purposes.

4. *Pediculosis* of the lashes may be treated by the mechanical removal of as many of the pediculi or nits as possible and by the local application of either a 3 per cent ammoniated mercury ointment or 0.25 per cent eserine salicylate ointment.

Conjunctiva

1. *General infections*—Most ocular infections due to bacteria should respond to the antibiotics now available. With the advent of the sulfonamides and the newer antibiotics, the continued use of yellow oxide of mercury has become obsolete. However, the correct use of these agents depends on familiarity with their pharmacologic action, and precautions should be taken in their usage. The choice of the appropriate drug depends on (1) the sensitivity of the organism to the drug; (2) the relative frequency of sensitization or allergic reaction of the individual to the drug, and (3) the presence or absence of purulent secretion against which sulfonamides (sodium sulamyd) are not effective.

Prior to starting therapy of any ocular infection, it is desirable and often imperative to get a smear, a culture and, possibly, sensitivity studies. Therapy is usually started with a sulfonamide or an antibiotic with which one is familiar. Ophthalmologists frequently give preference nowadays to the least toxic agent having a wide antibacterial spectrum such as sodium sulamyd, neomycin or one of the polymyxin-bacitracin group.

It is important not to sensitize the patient topically to a drug which he may need at some future time systemically. The most common abuse is the indiscriminate topical use of penicillin. If used at all, 100,000 units per gram should be used and not 1000 units per gram which may be of insufficient concentration to kill bacteria but sufficient to produce sensitization or cause an allergic dermatitis.

Clinical trial is the best test of the effectiveness of the antibiotic. If the ocular infection does not seem to be responding to the chosen antibiotic after 48 to 72 hours of therapy, change to another antibiotic. One may be guided by results of the culture, smear or sensitivity test taken at the onset of therapy. If the infection appears to be extending to the cornea or other parts of the eye, supplementary oral and parenteral therapy must be instituted.

The ointments of terramycin, AUREOMYCIN®, penicillin and streptomycin are much more stable than are their corresponding solutions.

(a) *Acute conjunctivitis* caused by various bacteria or viruses is best treated by antibiotic solutions. Ointments may be used overnight for prolonged effects, but as a rule they interfere with the profuse secretions and are best eliminated.

(b) *Chronic conjunctivitis* caused by *Staphylococcus* or by Morax-Axenfeld diplococcus must be treated vigorously and repeatedly. Ointments are better suited for this type of infection.

2. *Chemical burns of the eyes*—After initial thorough irrigation of the conjunctival sac, instillation of an ointment is indicated. Here also, frequent instillation of an oily solution such as castor oil is often used. For tear gas burns better results are obtained with a lotion than with a ointment. The lotion to be used consists of:

Sodium sulfite	0.4
Glycerin	75.0
Distilled water	100.0

This should be preceded by PONTOCAINE® anesthetic to prevent pain.

3. *Trauma or foreign body*—In cases of minor trauma or a foreign body in the conjunctiva, an antibiotic or sodium sulamyd ointment may be instilled as prophylaxis against infection.

Ophthalmic Ointment Medications

DRUG	CONCENTRATION	DRUG OF CHOICE IN	ALSO EFFECTIVE IN
Sulfonamides Topical Sodium sulamyd	10 per cent	Trachoma Inclusion blennorrhea Lymphogranuloma venereum Meningococcic infections	Gonorrheal infections *Escherichia coli* *Hemophilus influenzae* Beta hemolytic streptococci Actinomycosis Brucellosis Anthrax
Penicillin	1000 to 100,000 units per gram	Gonococcic infections *Staphylococcus* infections Alpha hemolytic streptococci Syphilis Actinomycosis and anthrax	Diphtheria conjunctivitis *Meningococcus* infections
Streptomycin or dihydrostreptomycin	5000 to 10,000 units per gram	Tuberculosis (with para-aminosalicylic acid) *E. coli* *H. influenzae* Morax-Axenfeld *Aerobacter aerogenes* *Proteus vulgaris*	*Bacillus pyocyaneus* ulcer Brucellosis
Aureomycin	5 mg. per gram	Brucellosis Tularemia	Gonococcic infections Herpes simplex? Herpes zoster? Virus infections
Terramycin	5 mg. per gram	Viruses	
Chloramphenicol (CHLOROMYCETIN®)	2.5 mg. per gram		
Neomycin	2.5 mg. per gram		
Bacitracin	500 to 1000 units per gram		
Polymyxin	1 to 5 mg. units per gram	*Pseudomonas aeruginosa (B. pyocyaneus)*	
Sodium proprionate	5 per cent	Seborrheic blepharitis	Most common eye pathogens, gram-negative or gram-positive
Mydriatic Atropine sulfate Scopolamine hydrobromide	½ to 1 per cent 0.2 per cent	Iritis; uveitis; refraction in children Epithelial ulcers of cornea	
Miotics Eserine salicylate Pilocarpine Vitamin A and D ointment	¼ per cent ½ to 1 per cent	Glaucoma Glaucoma; postoperative cataracts Epithelial ulcers of cornea	
Anesthetics Pontocaine BUTYN®	½ per cent ½ per cent		

Cornea

1. *Keratitis*—Inflammations of the cornea known as keratitis are best treated by the specific antibacterial or antiviral drugs—in ointment form if desired. In addition to measures already discussed, systemic medication is indicated. Because of its high concentration in the ocular tissues, as demonstrated by Leopold,[6] chloramphenicol is favored by many.

2. *Corneal foreign body*—Prophylactic use of an antibiotic following the removal of a foreign body from the cornea is good judgment. This, together with the use of a patch, is a necessity if the surface epithelium has been penetrated.

3. *Corneal ulcer or abrasion*—An antibiotic ointment and a patch are indicated. A mydriatic ointment, scopolamine hydrobromide 0.2 per cent, or atropine sulfate 1 per cent may also be used to good advantage. The pain associated with this condition is best controlled with aspirin, plus codeine, if necessary, rather than with topical applications of an anesthetic ointment or aqueous solution. The local anesthetic produces an inhibitory effect on healing. Disturbance of the patch for frequent instillations may also cause delayed healing of the ulcer.

4. *Burns* of the cornea are treated in the same way as corneal ulcer. In cases of cigaret burn, for instance, the entire epithelium may be sloughed off. An antibiotic to prevent infection plus a firm patch and a systemically administered analgesic will produce rapid healing. Some physicians advocate the instillation of an ointment preparation of vitamin A and D which is said to aid the regeneration of the corneal epithelium.

5. *Corneal dystrophies* are at times benefited by an ointment of 5 to 10 per cent sodium chloride in a base of anhydrous lanolin with petrolatum.

Iris and Ciliary Body

1. *Inflammations* of the iris and ciliary body—usually of an endogenous nature—take a more favorable course if these structures are immobilized by the use of 1 per cent atropine sulfate ointment (or solution). In addition, dilation of the pupil prevents the formation of adhesions between lens and iris. In the acute fibrinous or nongranulomatous types of iritis and iridocyclitis, the exudate in the anterior chamber is thick and fibrinous, and the tendency to formation of adhesions is greatest. In this type, therefore, a 1 per cent atropine sulfate ointment is used three to five times a day if necessary to dilate the pupil widely. In chronic cases of iridocyclitis, if sensitivity to atropine develops, an ointment of scopolamine hydrobromide 0.2 per cent is used.

Precautions should be taken with the use of atropine as a mydriatic. Many doctors inexperienced in the use of atropine have precipitated severe attacks of glaucoma. Some use this drug for minor injuries or abrasions to the eye. The indiscriminate use of the drug is an abuse of this ordinarily very useful and desirable medication. As a rule the contraindication to the use of this drug is the presence of a shallow anterior chamber with or without a history of attacks of elevated intraocular tension. In this type of patient one must inquire about symptoms of halos around lights, ocular pain or redness, dimming of vision after a movie, etc. This applies not only to the topical use of atropine but also to its parenteral or systemic use. It should be remembered also that the effects of one instillation of atropine last from 10 to 14 days.

Topical administration of an ointment of cortisone (CORTONE® 1.5 per cent) has been found to be effective in acute nongranulomatous iridocyclitis and many other acute inflammatory eye diseases. The pharmacologic effect of this medication is not the cure of any ocular disease but the protection of the ocular structures by blocking the destructive effects of the disease.

Cortisone is contraindicated in the presence of infection and in the early postoperative period when the wound healing may be delayed. In the first place, the presence of bacterial infection may be masked by the blocking effect on the inflammation. Specific antibiotic therapy must be used as adjuvant therapy; otherwise, on stopping the cortisone, the latent infection becomes overwhelmingly

manifest. Secondly, the cortisone may interfere with the early fibroblastic proliferation but does not interfere with those already laid down. In practice, cortisone may be given topically 8 to 10 days following surgery.

2. *Contusions and perforations of the globe*—In severe contusions use of a mydriatic such as atropine sulfate is also indicated. In perforations of the globe, ointment is contraindicated if there is a break in all the coats of the eye.

3. *Glaucoma*—Miotic ointments available for use in the treatment of glaucoma are 0.25 per cent eserine salicylate and 2 per cent pilocarpine nitrate. The former is frequently used at bedtime for control of intraocular tension during the night. The latter also is used postoperatively in cataract cases for its prolonged effect in constricting the pupil to prevent prolapse of the iris.

Summary

A brief description of ophthalmic ointments is presented together with a discussion of their correct use and of some mistakes commonly made. Some of the more common ocular diseases which are benefited by the use of topical ophthalmic ointments are described.

REFERENCES

1. Swan, K. C. and White, N. G.: Corneal permeability. Factors affecting penetration of drugs into the cornea. Am. J. Ophth. 25:1043, 1942.
2. Lehrfeld, L. and Donnelly, E. J.: Contaminated ophthalmic ointments. Arch. Ophth. 40:39 (July) 1948.
3. Sykowski, P.: Ointment in the anterior chamber. Am. J. Ophth. 33:800, 1950.
4. Smelser, G. K. and Ozanics, V.: Effects of local anesthetics on cell division and migration following thermal burns of the cornea. Arch. Ophth. 34:271, 1945.
5. Vail, D.: Gifford's Ocular Therapeutics. Philadelphia, Lea & Febiger, 1947.
6. Leopold, I. H.: Pharmacology and toxicology: annual review. Arch. Ophth. 46:159, 1951.
7. Dunphy, E. B.: Ocular therapeutic principles and practical applications. Arch. Ophth. 44:797, 1950.

Disturbances of Pulmonary Function in Rheumatic Heart Disease

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It would be simple if one could say that congestive heart failure with pulmonary edema is the only evidence of disturbed pulmonary function to be found in rheumatic heart disease, but such a statement unfortunately would omit from consideration many interesting and complex features of pulmonary alveolar and vascular pathologic physiology. The general practitioner has an enviable opportunity to witness many of these changes. He can be both spectator and actor in the full life story of the individual with rheumatic heart disease, and while observing the patient day by day and year by year he may encounter many of the problems to be discussed.

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The Alveoli

The alveoli of the lungs, with the alveolar walls, are deleteriously affected by a number of processes, beginning in some instances with the attack of acute rheumatic fever when a rheumatic pneumonitis may be found. This facet of the rheumatic state, controversial in its specificity,[1] has been seen in perhaps 10 per cent of cases of rheumatic fever.[2] It is a

feature of severe and not of mild cases and is accompanied by dyspnea and cough with minimal or no sputum in the absence of commensurate physical findings in the chest.[3] Roentgenograms of the chest show patchy areas of density, multilobular in distribution and evanescent in character (Figure 1). Under the microscope the picture is that of an anaphylactic angiitis with endothelial proliferation, hemorrhage and necrosis; Aschoff bodies may be found. Rich and Gregory[4] have discussed at length the anaphylactic experimental background of the lesions.

Pulmonary edema may occur as a reflection of acute myocardial weakness during the acute phase of the rheumatic state, as well as later on when this factor is abetted by specific aortic and mitral valvular deformities. Space does not allow a detailed discussion of pulmonary edema and its etiology. During the early phase, when some degree of interstitial edema of the alveolar and bronchial walls is present with consequent rigidity of the whole lung structure, the patient may seem to have asthma due to the wheezing type of respiration with prolonged expiratory note without actual rales. This "cardiac asthma" is all too often confused with bronchial asthma due to allergy, because of the similarity of physical findings; a proper distinction must be made if suitable therapy is to be instituted, and any patient with rheumatic fever or rheumatic heart disease and asthmatic type of breathing should be considered as having pulmonary congestion until proved otherwise.

With the appearance of frank accumulation of edema fluid and even red cells in the alveolar spaces (Figure 2), more profound dyspnea may occur and the characteristic moist rales appear. Sudden overwhelming edema is seen particularly in young female patients with tight mitral stenosis. It is often precipitated by the fluid retention present just prior to the menses, and the patient may literally drown in a few minutes. Such patients have been noted to have high resting "pulmonary capillary" pressure,[5] and marked rises in pressure occurring with stress or with increases in blood volume. With long-standing persistent edema, permanent alveolar changes

FIGURE 1. Roentgenogram of chest of a 7 year old boy with acute rheumatic fever including rheumatic pneumonitis. The arrows point to patchy areas of pneumonitis in the right middle and lower lung fields and in the left lower lung field. These areas resolved soon after salicylate therapy was instituted.

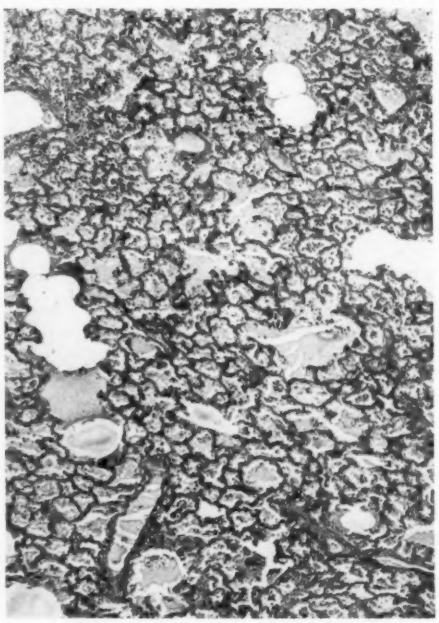

FIGURE 2. A low power view of a section of lung of a patient with rheumatic heart disease and subacute bacterial endocarditis dying with pulmonary edema, showing the alveolar spaces filled with edema fluid with some large "heart failure" cells and scattered red cells.

are encountered with fibrosis of the aveolar walls and changes in the capillary structure,[6] as well as with accumulation of focal clumps of hemosiderin which may be large enough to be visible on the roentgenogram;[7] the latter is rarely seen.

Should pulmonary infarction occur—and it is of interest that a congested lung is notably apt to develop infarction if embolism to the pulmonary arterial tree takes place[8]—the decreased blood supply and intra-alveolar hemorrhage will diminish or eliminate the possibility of aeration of the affected segment and thus contribute to respiratory embarrassment mechanically as well as by reflex pathways. Alveolar function may also be disturbed by accumulations of blood draining down from ruptured varicosities of the bronchial veins; by frank bacterial infection to which patients with advanced rheumatic heart disease are susceptible, and by compression atelectasis from large pleural effusions, from elevation of the diaphragm due to ascites and from massive enlargement of the left auricle. It appears that the last-named factor is relatively unimportant as a cause of dyspnea.[9]

The Bronchi

Disturbances in bronchial function are not as vital in the picture of rheumatic heart disease. Upward displacement of the left main bronchus due to enlargement of the left auricle is common in mitral stenosis, and some degree of bronchial compression may occur. Uncommonly, compression of the right middle lobe bronchus is seen, and an instance of collapse of the right middle lobe has been reported.[9] To what extent such bronchial pressure contributes to the persistent cough in advanced cases of rheumatic heart disease and how much is attributable to pulmonary congestion may be difficult to say in a given case. Chronic bronchial infection engendered by weakness of the patient and subsequent difficulty in raising bronchial secretions may also play a role.

The Pleural Cavities

The pleural surfaces and pleural cavities deserve mention also. The fibrinous pleurisy which may accompany acute rheumatic fever is not in itself of great functional significance except as a source of pain which may limit thoracic excursion. More important is the accumulation of pleural fluid observed in advanced cases of aortic, mitral and combined valve diseases. Such a hydrothorax is more common on the right side than on the left. It may interfere with respiratory function by decreasing the amount of functional residual and reserve air,[10] and contribute to the elevation of venous pressure. The benefit to the patient's breathing comfort derived from the removal of a large quantity of pleural fluid is well known to every physician. It should not be forgotten that the existence of a pleural effusion may be a clue to the presence of pulmonary infarction.

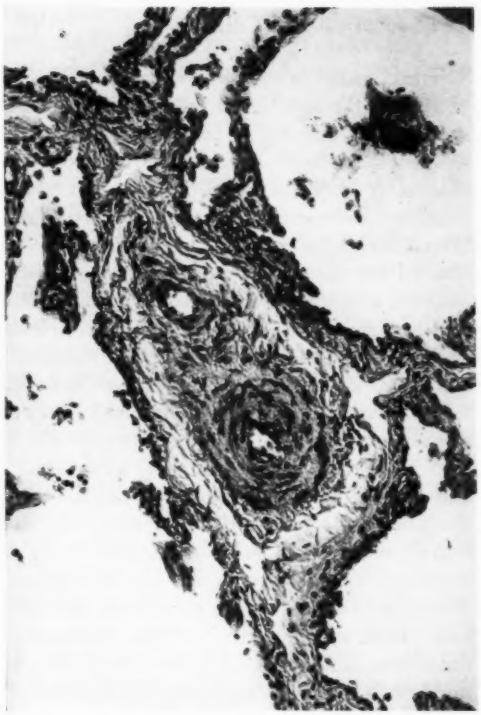

FIGURE 3. Pulmonary arterioles from the lung of a 36 year old patient who had rheumatic heart disease with a high degree of mitral stenosis. The arterioles, as well as one capillary, show hyperplasia of the walls with both medial and intimal hypertrophy of the arteriolar walls. The lumen of each arteriole is reduced in size.

The Pulmonary Vessels

The changes in the pulmonary vascular bed are one of the most interesting aspects of rheumatic heart disease. It is not surprising that extensive vascular changes are found in a disease in which increased pulmonary arterial, capillary and venous pressures may be maintained for years. Parker and Weiss[11] in 1936 studied the pulmonary vascular bed in mitral stenosis and described a group of histologic findings including hyperplastic arteriosclerosis, intimal arterial thickening, thickened capillary basement membranes, alveolar capillary dilatation, and collagenous thickening of the alveolar walls. More recently other workers[12,13] have commented on these observations and stressed medial muscular hypertrophy in the arteries as an important finding in both mitral stenosis and mitral regurgitation. The extent of these microscopic changes (Figure 3) might well lead to the belief that their diffuse nature would result in severe irreversible functional alterations. That this is not entirely the case is obvious from the fact that mitral valve surgery, even in patients with advanced disease, may bring dramatic improvement over the course of months with remarkable reduction postoperatively in the pulmonary arterial pressure. Even greater clinical recovery may, however, be prevented by the vascular damage already described as well as by irreversible changes in the myocardium itself.

Pulmonary infarction is a most important subject and has already been discussed in part. Emboli arising in the fibrillating right auricle or from the leg or pelvic veins may be the critical factor in precipitating congestive heart failure, or in other instances will so aggravate a chronic state of cardiac decompensation that an early death ensues. The possibility of pulmonary infarction is too seldom considered clinically still; it may be detected by a careful routine search for a source of thromboembolism in the leg veins, by studying the roentgenograms of the chest and by paying special attention to episodes of chest pain, hemoptysis, unexplained fever and unexplained tachycardia. A single large pulmonary artery may be occluded with immediate disastrous results or, more often, several vessels of smaller size are involved; this, in turn, leads to a reduction in function of pulmonary tissue and at times to an aggravation of pulmonary arterial hypertension. As has been pointed out, such pulmonary arterial occlusion is most often seen in patients who already have frank or impending cardiac decompensation. The reduction in pulmonary arterial flow may also be accompanied by pulmonary venous thrombosis, causing a further deterioration in the integrity of the pulmonary vascular bed and conceivably even providing a source of peripheral embolism.

Also deserving of mention is the existence in certain patients with mitral stenosis of large, direct communications between the bronchial and pulmonary venous systems. It has been thought[14] that hemoptysis in patients with mitral stenosis is due to rupture of one of these bronchial varicosities.

Treatment

The treatment of rheumatic pneumonitis is the treatment of acute rheumatic fever itself, a subject which will not be discussed in this article. The value of oxygen, salicylates in adequate dosage and of ACTH and cortisone in controlling the symptoms and certain clinical features is well known. Attention may properly be directed to one phase of drug therapy which may in itself produce respiratory symptoms, namely, the hyperpnea accompanying intensive salicylate therapy. It is important to consider the toxic effect of salicylates in the differential diagnosis of respiratory distress which occurs in the course of treating rheumatic fever, and if there is a question as to salicylate intoxication the dosage should be sharply curtailed.

Treatment directed toward the control of pulmonary edema occurring in acute rheumatic fever must depend on a combination of methods. Physical rest and the use of oxygen are, of course, important, but when symptoms or signs of pulmonary congestion with oxygen lack are found—and restlessness may often be the first clue to its presence—prompt resort should be made to the use of diuretics.

A valuable oral diuretic and one which is usually well tolerated by the gastrointestinal tract is THEOCALCIN®, which can be given both to children and to adults in doses of 0.5 to 1.0 gm. four times a day. Ammonium chloride may be undesirable in these circumstances because of its tendency to produce nausea in the acutely ill patient. When a more rapid-acting preparation is desirable, MERCUHYDRIN® or THIOMERIN® in doses of 0.25 to 1.5 cc. intramuscularly or subcutaneously may be lifesaving and often should be repeated every other day until evidences of a recovery of cardiac compensation are seen. Large doses of mercurial diuretics are usually unnecessary and unwise; it is better to give small doses more frequently than to administer large amounts infrequently. Digitalis preparations are not of striking value in any type of active myocarditis, but may be used if diuretics and oxygen prove inadequate to control pulmonary congestion or if auricular fibrillation or flutter is present.

A low sodium diet, while theoretically desirable when cardiac decompensation occurs in rheumatic fever, should be used with discretion; it is excellent if well tolerated, but when it results in a refusal of meals it is wiser either to compromise and permit a more liberal sodium intake or to enlist the services of a dietitian who can prepare an attractive menu within the restrictions of the diet (and this can be done).

In the patient with established rheumatic heart disease the control of pulmonary edema requires a different approach, for here the physician must think in terms of a long-term program. First, what has brought on pulmonary edema? If it is the onset of auricular fibrillation, adequate digitalization may solve the problem for the time being. If it is a respiratory infection or subacute bacterial endocarditis, antibiotics are indicated. If it is pulmonary infarction, anticoagulants should be employed, as will be discussed later. If it is active rheumatic fever, the patient must be treated like any other patient with an active rheumatic myocarditis—with proper rest, protection from exposure to upper respiratory infections, etc. If it is exhausting physical effort, the patient needs guidance in his future activities.

Given the problem of chronic and recurring pulmonary edema, whatever the exact basis, there is one firm rule that applies: Since this is a chronic difficulty, therapy must be planned on a preventive basis. It is disastrous to wait and treat each attack of pulmonary edema when it occurs—the aim should be to prevent attacks. Mild symptoms can often be controlled on a combination of moderate sodium restriction (2 to 3 gm. of sodium chloride a day) plus an oral diuretic (in adults, ammonium chloride in doses of 4 to 6 gm. daily for 10 days every two weeks is excellent) plus digitalis. The simple maneuver of elevating the bed 4 to 6 inches on blocks may prevent nocturnal dyspnea.

When it is apparent that such measures applied continuously are inadequate, it is wise to insist on a strict low sodium diet (0.5 to 1.0 gm. of sodium chloride a day), digitalis, ammonium chloride and regular doses of a mercurial preparation. The optimal interval between injections of the mercurial diuretic can be judged by following the weight every day. A gain of 2 or more pounds is a warning signal that an injection is needed. It has been my experience that many patients can be taught to give thiomerin or mercuhydrin to themselves; if the patient is unable to take on this responsibility, some member of the family usually is willing to learn the technic.

In an acute attack of pulmonary edema the following measures are helpful: (1) Place the patient in a sitting position; (2) administer oxygen if available; (3) apply tourniquets to the lower limbs just below the groins and to one arm just below the axilla (this is usually preferable to attempting a phlebotomy, which is not always readily accomplished); (4) give 8 mg. of morphine intravenously and 8 mg. subcutaneously; (5) give 250 mg. of aminophylline intravenously, slowly; (6) if the patient is not already receiving digitalis and has not rallied in the first 15 to 20 minutes of this routine, or if uncontrolled auricular fibrillation or flutter is present, administer ouabain in doses of 0.5 to 0.75 mg. intravenously; (7) it is usually wise, after these emergency

measures, to administer a mercurial diuretic intramuscularly.

Before leaving the subject of pulmonary edema in rheumatic heart disease, the proved value of mitral commissurotomy in relieving pulmonary congestion in certain cases must be emphasized. Patients whose chief valvular deformity is mitral stenosis may be rehabilitated to a striking degree by properly executed surgery. Careful postoperative physiologic studies have shown highly significant reductions in pulmonary arterial and "pulmonary capillary" pressures. Furthermore, even without such laboratory evidence, the patients themselves provide irrefutable proof of the benefit of the operation—improved exercise tolerance, relief of dyspnea and orthopnea and disappearance of recurrent hemoptysis.

The treatment of pulmonary infarction in rheumatic heart disease is not an easy matter. There is little question that the careful use of DICUMAROL® or tromexan is of value in the control of thromboembolic phenomena, provided suitable laboratory control is available. (Heparin may also be employed but is only suitable for short-term therapy.) These drugs have the advantage of controlling thrombus formation in both the leg veins and the right auricle, sites from which pulmonary emboli arise; they have the disadvantage that once treatment is started it cannot be stopped without the hazard of prompt recurrence of embolic phenomena.

An alternative form of therapy is ligation of both femoral veins. This may be employed if there is reasonable evidence that the source of pulmonary emboli is in the deep veins of the legs. It should be pointed out that neither form of treatment is invariably effective in providing complete protection, partly due to difficulties in maintaining proper control of the prothrombin level (a level of 15 to 30 per cent is optimal) and partly because thrombi are sometimes present or form above the site of venous ligation. Nevertheless it should be stressed that once the diagnosis of pulmonary infarction is made it is incumbent upon the attending physician to employ one of the forms of treatment already described.

A final word should be said regarding bronchial and parenchymal pulmonary infection. It is well known that patients with rheumatic fever or rheumatic heart disease are susceptible to such infection, that the infection itself is a potent source of aggravation of congestive heart failure and that a reactivation of rheumatic fever may occur. It is thus evident that prompt use of penicillin given intramuscularly in minimal daily doses of 600,000 units is indicated once evidence of active bronchial or pulmonary bacterial infection is found; blood and sputum cultures taken just prior to initiation of such therapy may later indicate that some agent other than penicillin is to be preferred. However, there is no antibiotic preparation superior to penicillin for immediate use under these circumstances, and the drug should be continued for 10 or more days if studies indicate a beta hemolytic streptococcal infection.

We have found it both practical and safe to institute therapy with either dicumarol or tromexan in the hospital, initially taking two-stage prothrombin levels daily, and then continue treatment indefinitely on an ambulatory outpatient basis. At the end of a month, most patients only require prothrombin determinations every two weeks and several dozen have now been carried along safely in this fashion for many years, thanks to the invaluable assistance of Dr. John Olwin and his laboratory.

REFERENCES

1. Friedberg, C. K.: Diseases of the Heart. Philadelphia, W. B. Saunders Company, 1949, p. 734.
2. Griffith, G. C., Phillips, A. W. and Asher, C.: Pneumonitis occurring in rheumatic fever. Am. J. M. Sc. 212:22, 1946.
3. Seldin, D. W., Kaplan, H. S. and Bunting, H.: Rheumatic pneumonia. Ann. Int. Med. 26:496, 1947.
4. Rich, A. R. and Gregory, J. E.: On the anaphylactic nature of rheumatic pneumonitis. Bull. Johns Hopkins Hosp. 73:465, 1943.
5. Gorlin, R., Haynes, F. W. and Dexter, L.: Pathogenesis of pulmonary edema in mitral stenosis. Am. J. Med. 10:234, 1951.
6. Weiss, S.: Pulmonary congestion and edema. Bull. New York Acad. Med. 18:93, 1942.
7. Pendergrass, E. P., Lame, E. L. and Ostrum, H. W.: Hemosiderosis of the lung due to mitral stenosis: A report of six cases simulating pneumoconiosis. Am. J. Roentgenol. 61:443, 1949.
8. Chapman, D. W., Gugle, L. J. and Wheeler, P. W.: Experimental pulmonary infarction: Abnormal pulmonary circulation as a prerequisite for pulmonary infarction following an embolus. Arch. Int. Med. 83:158, 1949.
9. Daley, R. and Franks, R.: Massive dilatation of the left auricle. Quart. J. Med. 18:81, 1949.
10. Altschule, M. D. and Zamcheck, N.: The effects of pleural effusion on respiration and circulation in man. J. Clin. Investigation 23:325, 1944.
11. Parker, F., Jr. and Weiss, S.: The nature and significance of the structural changes in the lungs in mitral stenosis. Am. J. Path. 12:573, 1936.
12. Larrabee, R. L., Parker, R. L. and Edwards, J. E.: Pathology of intrapulmonary arteries and arterioles in mitral stenosis. Proc. Staff Meet., Mayo Clin. 24:316, 1949.
13. Becker, D. L., Burchell, H. B. and Edwards, J. E.: Pathology of the pulmonary vascular tree. II. The occurrence in mitral insufficiency of occlusive pulmonary vascular lesions. Circulation 3:230, 1951.
14. Ferguson, F. C., Kobilak, R. E. and Deitrick, J. E.: Varices of the bronchial veins as a source of hemoptysis in mitral stenosis. Am. Heart J. 28:445, 1944.

Pediatrics IN GENERAL PRACTICE

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Drugs Used in Pediatric Allergy

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S. C. SIEGEL

WITH one notable exception, very little that is new and of value has been added to the pediatric allergist's drug armamentarium during the past two or three years. The exception, of course, is the use of adrenocorticotropic hormone (ACTH) and cortisone in the treatment of allergic conditions.

Immediately following early reports of dramatic results in treating practically all types of allergic conditions with ACTH or cortisone, use of the drugs became very popular. However, most investigators quickly realized that these hormones were not a panacea for allergic patients.[1-3] Nevertheless, ACTH and cortisone have taken their place among the more useful adjuncts in the treatment of certain allergic diseases—bronchial asthma, seasonal and perennial allergic rhinitis, serum sickness, drug sensitivities, urticaria, angioneurotic edema, atopic eczema and contact dermatitis.

In a previous paper[1] my co-workers and I expressed our opinions on the use of ACTH and cortisone in the treatment of asthma and eczema. Briefly, these opinions can be summarized as follows:

1. Both hormones are potent agents for the temporary relief of these conditions.
2. Dosage for infants and children is relatively large as compared with adult dosages and is somewhat dependent on the severity of the illness.
3. The hormones have very little effect on skin test reactions.
4. No serious ill effects in patients were noted.
5. Finally, it was emphasized that the drugs are potentially just as harmful as they are good and that they should be given only under close supervision.

Further experience with these hormones has confirmed most of our earlier impressions. The general doses of cortisone now employed for older children are 100 mg. daily,

given either orally or parenterally, until symptoms have subsided. Then the amount is gradually tapered to a maintenance dose of 25 to 50 mg. or is discontinued completely. ACTH is given in quantities of about 40 mg. a day. A slow-absorbing product, ACTHAR® Gel (Armour), also has become available. Recently, reports have been appearing showing that small doses of crystalline ACTH, 10 to 15 mg. administered by intravenous drip, are as effective as the larger doses given intramuscularly.[2-4] For infants, depending on their size and the severity of the disease, about one-third to one-half the doses for older children of either drug are used. The amounts are always adjusted to the response of the patients and kept at the smallest dosage that will maintain the patients free of symptoms.

Although no serious ill effects have been experienced by any of my patients to date, the many reports in the literature of the side effects—sometimes quite dangerous—from the use of these hormones should be a deterrent to their indiscriminate use. In carefully selected patients who have not responded to older symptomatic methods, ACTH and cortisone can often be used with excellent results. Under no circumstances should they be used as a substitute for past methods of allergic management—but only as an additional tool for symptomatic relief.

Antihistamines

Although the antihistaminic drugs can no longer be considered new, and though their peak of "popularity" has fallen, they are still useful drugs in the management of allergic patients. They are best used in the treatment of pollinosis, perennial allergic rhinitis and urticaria; they are relatively ineffective in eczema and asthma.

The list of good antihistamines is long and is still growing. However, few of those recently introduced are superior to the older, more thoroughly investigated compounds.

One of the newer antihistamines which I have found to be very effective is PHENERGAN® (Wyeth). It has the advantage of long action, and it need be given only at bedtime. Its side effect of sedation is helpful through the night and usually does not persist through the next day. Doses employed have been 12.5 to 25 mg. The drug is now available in a palatable liquid form for children.

When one of these antihistamines fails to produce a good response, another with a different chemical structure should be tried. However, it is not the purpose of this paper to review the relative merits of the popularly used antihistamines, since many excellent reviews have been published.[5,6]

The use of antihistamines, especially in children, is not without danger. Over half of the severe intoxications that have been reported have occurred in children. Most of these were due to accidental ingestion of large quantities of the drugs. Lecks[7] has written an excellent review of antihistamine intoxication in children, including a well formulated plan for treatment of such patients.

Epinephrine and Ephedrine

Although neither epinephrine nor ephedrine is new, they must be included in any presentation on the use of drugs in the treatment of allergy. Most allergists are agreed that these agents still rank among the best drugs for symptomatic relief, but they are sometimes forgotten in the haste to try everything that is new.

In spite of proved effectiveness, epinephrine and similar compounds have their disadvantages: They must be injected or inhaled; they act for only a short period of time and often produce unpleasant side reactions, such as tremor and palpitation. One compound which eliminates some of these latter disadvantages is BUTANEFRINE® (Winthrop-Stearns). It is used in approximately twice the dose of 1:1000 epinephrine. Usually 0.2 to 0.5 cc. will suffice and give as good results, with the same duration of action, as ADRENALIN®.

For longer effects, adrenalin, 1:500 in oil given intramuscularly, has long been used. Recently, to obviate some disadvantages of this preparation, a new substitute, SUSPHRINE® (Brewer) has become available. It consists of a 1:200 suspension of epinephrine which can be given subcutaneously with a tuberculin syringe and a 26 gauge or

27 gauge needle. The advantages over adrenalin in oil are ease of administration, relative painlessness and greater economy. Unger and Unger[8] have used this preparation in 173 patients and the vast majority preferred susphrine to adrenalin in oil. I have had some experience with this preparation and also have found it to be a valuable therapeutic aid for persons with asthma and chronic urticaria. The dose used in children has been 0.1 to 0.3 cc.

Ephedrine is still probably one of the most widely used drugs for asthma and hay fever. It has the advantage of being effective when taken orally. Usually it is combined with a barbiturate to counteract its side effects, and with a xanthine type of drug to enhance its effectiveness. Literally dozens of these compounds are available to the physician. One should be acquainted with just a few of them so as to be familiar with their contents, actions and possible side effects.

Other sympathomimetic drugs which have effects similar to those of ephedrine are NETHAMINE® (Merrill) and ORTHOXINE® (Upjohn). The former has been combined with a xanthine and DECAPRYN® and marketed under the name NETHAPRIN®. Hansel[9] reported this drug to be very effective in bronchial asthma. He recommended that older children take 1 capsule or teaspoonful three times a day.

Orthoxine is also very effective in persons with mild asthma. Each teaspoonful of the syrup contains 10 mg. of the drug and it is given to infants in doses of ¼ to 1 teaspoonful every three to four hours. Older children usually can tolerate ½ to 1 tablet, each tablet containing 100 mg. of orthoxine.

Xanthines

Xanthines also rank high as therapeutic agents in the relief of asthma. One of the most commonly used is aminophylline, which can be given intravenously, orally or rectally. As already mentioned, when given by the latter two routes, it is often combined with a sympathomimetic drug and a sedative. In infants it is best given in suppository form in doses of approximately 0.125 gm. every six hours. Older children often tolerate 0.25 gm. but if this dose is exceeded, nausea and vomiting often occur.

Expectorants

Any discussion of drugs used in allergy is incomplete unless the expectorants are included. Most important of these is the old remedy, potassium iodide. This can be given in the form of enteric-coated tablets or in a saturated solution—10 drops three times a day. Children, however, have difficulty swallowing the tablets and dislike the taste of the solution. As substitutes, other types of iodides and combinations are available and are sometimes better taken. Syrup hydriodic acid mixed with cherry base, CALCIDRINE® (Abbott), LOBIDINE® (Searle) and BRACODIN® (McNeil) have all been used effectively. Ammonium chloride or syrup of ipecac can also be substituted.

Pyromen

In 1950 Randolph and Rollins[10] reported on an entirely new type of drug for the treatment of allergic conditions. This drug—PYROMEN® (Baxter)—is, according to the manufacturer's definition, a sterile, nonprotein, nonanaphylactogenic, bacterial component, thought to be a complex polysaccharide. It is administered in doses of 1 to 5 mcg. subcutaneously two to three times a week. In these doses pyromen has been reported as being therapeutically effective in asthma, hay fever, atopic dermatitis, urticaria, gastrointestinal allergy and fatigue syndrome of allergic origin.[10-13]

To date, I have seen neither adverse reports nor favorable findings in an adequately controlled study. Pyromen should be considered as still under investigation, and until more extensive controlled clinical studies have proved its worth it should be used only with that thought in mind.

Summary and Conclusions

A brief review of the more commonly employed drugs used in pediatric allergic conditions has been presented. Of the new drugs that have become available in the past two or

three years, only ACTH and cortisone have been proved definitely to be useful adjuncts in the treatment of allergic conditions. Pyromen has still to be evaluated critically. As yet, no drugs have appeared which can obviate the necessity for a good allergic workup and allergic management.

REFERENCES

1. Glaser, J., Siegel, S. C., Goldstein, J. D. and Meltzer, R. S.: Experiences with ACTH and cortisone in the treatment of asthma and eczema in infancy and childhood. Ann. Allergy 9:292, 1951.
2. Abbesman, C. E.: Recent advances in treatment of bronchial asthma. New York State J. Med. 51:2361-2369 (October 15) 1951.
3. Hampton, S. F.: Intravenous ACTH in treatment of allergic diseases. Presented at the meeting of the American Academy of Allergy, February 1952.
4. Segal, M. S., Hershfus, J. A. and Levinson, L.: ACTH and chronic bronchial asthma. G.P. 3:33, 1951.
5. Feinberg, S. M., Malkiel, S. and Feinberg, A. R.: The Antihistaminics, Their Clinical Application. Chicago, The Year Book Publishers, Inc., 1950.
6. Britton, C. J. C.: The antihistaminic drugs. Practitioner 164:457, 1950.
7. Lecks, H. I.: Acute antihistamine intoxication in childhood; suggestions for antidotal therapy. Quart. Rev. Pediat. 6:294, 1951.
8. Unger, A. H. and Unger, L.: Prolonged epinephrine action; a report on use of epinephrine suspension. Ann. Allergy 10:128, 1952.
9. Hansel, F. K.: Nethaprin in the treatment of respiratory allergy. Ann. Allergy 8:745, 1950.
10. Randolph, T. G. and Rollins, J. P.: Pyromen in the treatment of perennial allergic symptoms. Ann. Allergy 8:626, 1950.
11. Wittich, F. W.: Pyromen in the treatment of perennial respiratory allergies. Ann. Allergy 9:502, 1951.
12. Zindler, G. A.: Pyromen therapy in the treatment of food allergy; a preliminary report. Ann. Allergy 9:494, 1951.
13. Guerrieri, J. A.: Treatment of neurodermatitis with pyromen, a new therapeutic agent. Clin. Med. 59:29, 1952.

Treatment of Fibrosis of the Pancreas

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The adequate treatment of patients with fibrosis of the pancreas must begin with accurate diagnosis. Suspicion must precede appropriate diagnostic methods. Although at one time this disease was considered rare and unusual, it is becoming apparent to most physicians who see many children that it is a not uncommon syndrome. Since it is inherited as a recessive characteristic, one can estimate the approximate incidence of the disease. The gene frequency among the population of the United States is somewhere within the limits of 2 per hundred to 18 per hundred persons, and thus roughly one in a thousand live births will represent children with fibrosis of the pancreas.[1]

Diagnosis

Suspicion of the disease should form in the mind of a physician when he is called to attend an infant in the first two months of life because of chronic respiratory complaints. These may be as simple as wheezing or as severe as recurrent pneumonitis. Characteristically, the patient has but mild fever, does not appear seriously ill and continues to eat well in spite of cough and dyspnea.

A second symptom requiring attention is failure to regain birth weight, in the absence of other obvious cause, after the first 14 days of life. Following the physiologic neonatal weight loss, most infants regain their birth weight by 10 days; patients with fibrosis of the pancreas may require from two to eight weeks to do so.

Among the newborn, a physician should be suspicious of any patient who fails to pass meconium readily or in whom a roentgenogram of the abdomen, while indicating intestinal obstruction, also demonstrates multiple loops of bowel filled with frothy, spongelike material.[2] Such patients have fibrosis of the pancreas and meconium ileus—intestinal obstruction secondary to the presence of inspissated sticky meconium.[3]

The mother of a patient with fibrosis of

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the pancreas seldom comes to a physician because an infant's stool is abnormal, as infants with this disease do not characteristically have diarrheal stools. Rather their dejecta is bulky and the total amount passed per day is large; however, this is a sign which infrequently seems to concern parents.

The index of suspicion increases in children 1 to 3 years of age for whom there is a history of chronic nutritional failure, abnormal stools and respiratory complaints. The two most helpful bits of data in evaluating such patients are the history of a voracious appetite and the finding of *Staphylococcus aureus* in the nose and throat of a patient not yet treated with chemotherapeutic agents. With an appropriate history, it is frequently possible to be relatively certain clinically that a patient suffers from fibrosis of the pancreas. Furthermore, if a history of this disease among siblings can be obtained, the diagnosis seems almost positive.

Roentgenographic examination of the lungs can be diagnostic early in the disease, particularly in the hands of radiologists who are familiar with the expected changes. Neuhauser[2] has stressed that one should look for emphysema with bulging of the rib interspaces which is random in distribution. Added to this are scattered atelectasis and areas of peribronchial infiltration.

The single laboratory test most helpful in making a definitive diagnosis is the demonstration that normal tryptic activity in the duodenum is lacking. Unfortunately there are no specific chemical tests for trypsin, and the physician is dependent on certain properties of trypsin for determining its presence. The specific property used in most laboratory tests depends on the fact that trypsin can hydrolyze native protein while the other ferments of the bowel, particularly pepsin and erepsin, can hydrolyze only partially denatured protein. Furthermore, trypsin is active in alkaline mediums while pepsin is active only in an acid menstruum.

Gelatin is the commonly used substrate for the demonstration of tryptic activity, for once affected by trypsin, gelatin will no longer form a solid gel at icebox temperatures. Unfortunately, bacteria are occasionally present in the small bowel which elaborate an enzyme capable of denaturing and hydrolyzing gelatin.[4] These bacterial enzymes are called gelatinases, and in laboratory determinations for tryptic activity it is impossible to differentiate the activity of a gelatinase from that of human trypsin. The work of Johnstone[5] has helped to clarify this problem. Those organisms which tend to elaborate a gelatinase and which tend to appear in patients receiving chemotherapy are largely gram-negative bacilli. One may inhibit normal trypsin and not inhibit bacterial gelatinase by the incorporation of a soybean trypsin inhibitor in the test solutions, and by this means get information concerning the presence of gelatinase.

It is obvious that it becomes imperative to culture any duodenal material before accepting completely the results of trypsin assay, for if gram-negative bacilli are abundantly present, apparent tryptic activity may represent only bacterial gelatinases. Shwachman[6] has reported that the viscosity of the fluid obtained from the duodenum of patients with fibrosis of the pancreas is greater than that obtained from normal individuals. Viscosimetric methods have been used by him to aid in making the diagnosis of fibrosis of the pancreas. However, it seems probable that this is not a definitive test. Microscopic examination of the pancreas of patients dying of fibrosis of the pancreas indicates that it is highly improbable that any secretion can reach the duodenum from affected acini, so that if the duodenal fluid is of increased viscosity this increase is not due to abnormal pancreatic juice. Furthermore, Baggenstoss and associates[7] recently have suggested that the duct system of the pancreas in an afflicted patient is such that it would be impossible for secretions, viscid or otherwise, to reach the lumen of the bowel. Thus the observation of increased viscosity is interesting and may be helpful, but should probably not be used as a definitive laboratory test.

Johnstone, by improving on the original suggestion of Shwachman, has attempted to offer a scientific basis for a stool test for trypsin.[5] This method obviates intestinal in-

tubation and may prove to be a simple yet definitive test for fibrosis of the pancreas. The precaution already mentioned concerning bacterial gelatinases is even more applicable when doing stool trypsin determinations. However, it seems probable that with appropriate precautions this test can be used.

Numerous other metabolic and chemical abnormalities can be demonstrated in patients with fibrosis of the pancreas: the poor absorption of vitamin A;[7] the failure to demonstrate an increase in the amino acid level in the blood after ingestion of a protein meal,[9] and azotorrhea and steatorrhea.[10,11] Each of these abnormalities may exist, but probably the demonstration of none is necessary for a final diagnosis. Occasionally, however, a stool nitrogen determination should be performed, particularly if the results of trypsin determination are equivocal. Shohl and co-workers[10] have offered the most important and convincing evidence on this point, and have set the normal limits for stool nitrogen. The stools of normal infants contain less than 0.4 gm. of nitrogen per day, while for older children this figure is 1 gm. per day. Roughly 40 per cent of the nitrogen excretion occurs via the stool in patients with fibrosis of the pancreas, while for normal subjects this figure is only 15 per cent.

Treatment

When the diagnosis is well established, the physician then faces the problem of providing therapy directed at correcting (1) recurrent respiratory tract infections and (2) the nutrition of the patient. The latter offers few difficulties, but the former poses many problems and its severity probably determines the prognosis of the patient. While the disease should not be divided into types and subtypes, it becomes obvious when observing a patient with fibrosis of the pancreas that at different periods of life different problems appear and different types of therapy may be used.

When meconium ileus is diagnosed in a newborn, a simple Mikulicz enterostomy may be performed. The point of ileostomy frequently is quite high and must be made where normal bowel can be demonstrated. It is frequently possible at laparotomy to irrigate the ileum with a 1 per cent solution of pancreatin U.S.P. and in this way remove viscid meconium. When the bowel can be completely freed of viscid meconium, by either saline or pancreatin irrigation, ileostomy can be avoided and, following ileotomy, the intact bowel left in the abdomen. That this procedure can result in a successful outcome has already been demonstrated.[12]

In some patients whose family history records that siblings have had fibrosis of the pancreas, it is possible to be suspicious of this disease very early in life. The attending physician may note that the patient is not gaining weight at a rate which might be anticipated. Most children who have fibrosis of the pancreas gain weight poorly the first three months of life.[13] As one observes them, one cannot help but feel during this period that they make some metabolic adjustment to their digestive disability, for frequently by the end of four or five months they may be gaining weight at a normal rate. Although definitive evidence is not available to confirm the point, it seems possible that during this period infants will gain weight better if supplied with a predigested protein product such as NUTRAMIGEN.® However, if an infant's caloric intake is better on a whole milk modification than it is on an artificial formula, it probably is wise to use the former. The use of pancreatin in this age group seems unnecessary, and it is doubtful that prophylaxis with present day chemotherapy will prevent the onset of respiratory diseases.

Once an adequate weight gain has been established—and this may almost always be anticipated—it has been our practice to provide children with a normal diet for their age with the provision that this be offered ad libitum. We have not used pancreatin, since it tends to decrease appetite and, although it increases fat and nitrogen absorption, there is little evidence that it increases the total caloric absorption or nitrogen retention.[14]

Respiratory complaints should be treated at the time they appear, since anticipation and prophylaxis in our experience have not been successful. The drugs of choice seem to

be either AUREOMYCIN® or terramycin, given in doses up to 50 mg. per kilogram of body weight per day. Although patients in this age group may have wheezing as a complaint, or as a finding on physical examination, bronchial dilators have not been particularly helpful.

Since the pathologic changes in the lungs of patients with this affliction may be caused by blockage of bronchioles by secretions, the elimination of these secretions seems important. Where at one time it was considered sufficient to supply chemotherapeutic assistance by aerosol, through the years it has become apparent that this in itself is not entirely effective. Administration by the aerosol route of enzymes calculated to liquefy these secretions has been attempted. We have used mucinase, a mucolytic enzyme; streptodornase plus streptokinase; an alkaline medium such as a dilute sodium bicarbonate, and dilute solutions of pancreatin U.S.P. Bruyn[15] has employed TRYPTAR® (Armour). None of these has been dramatically successful, yet in some patients the use of each has been attended by some improvement. It seems almost axiomatic that the finding of an appropriate lytic agent for the secretions in the respiratory tract of these patients will prove of dramatic help.

The secretions already mentioned lead to emphysema, and eventually the emphysema becomes so distressing, extreme and chronic that it leads to cor pulmonale and heart failure. This is a complication of fibrosis of the pancreas rarely seen under 4 years of age and not uncommonly seen in older children.[16] An attractive hypothesis suggests that the cor pulmonale is a reflection of alveolar pressure which is greater than the venous pressure in the pulmonary capillaries. If this is correct, these patients should have predominantly right-sided heart failure, and clinically one commonly observes this. The lungs remain surprisingly dry in the face of peripheral edema and even anasarca. The heart failure associated with cor pulmonale responds to digitalis and mercurial diuretics, for edema will disappear and heart size decrease following such medication.

When pulmonary infection accompanies the decompensation, it too must be vigorously treated. A low salt diet appears neither to aid in getting rid of edema nor to decrease its rate of accumulation. Once cor pulmonale has appeared, the patient's prognosis is extremely poor and most of those afflicted expire within a year of the onset of this complication. However, many children will have multiple episodes of decompensation and recovery, suggesting that each recurrence is related to acute infection and each remission to a resolution of the infection.

Although the use of pancreatin does not seem advisable in younger children, as a child gets older his voracious appetite and the large amount of stool passed become annoying, and it is then possible to use pancreatin to alleviate these two distressing complaints, since it will decrease appetite and stool volume. However, we have not observed any specific benefit from its use as far as general health or nutrition is concerned. If pancreatin is used, one should avoid homeopathy. A dose of from 6 to 12 gm. per day ought to be used between the ages of 4 and 12. This dose level is based on the fact that adults, following surgical removal of the pancreas, require up to 20 gm. of pancreatin a day for optimal fat and nitrogen absorption.[17] Furthermore, there seems to be no evidence that administration of pancreatin in any way influences the ultimate course of the disease in children.

In conjunction with this attitude toward pancreatin, we have adopted a philosophy toward diet which permits patients to eat what they will. No attempt is made to limit fat or carbohydrate in the diet. There has been ample indication that the more fat these patients are fed, the more they absorb. Washing-out of essential nutrients such as protein by fat has not been observed.[14]

Supplemental vitamins seem to be necessary. Fat-soluble vitamins are poorly absorbed;[8] hence, vitamins A and D should be administered in doses of two or three times the amount required by normal children. While the absorption curves obtained with vitamin A are better when an emulsified or water-miscible form of vitamin A is used,[18] there is little evidence that the clinical course

of patients to whom it is administered is in any way superior to that of patients receiving an oily preparation of vitamin A in adequate amounts. Furthermore, vitamin A seems to be more stable in percomorph oil than in alcoholic solutions, and this in itself would indicate that this type of preparation is preferable. The need for extra amounts of the water-soluble vitamins, both the B group and vitamin C, has not been demonstrated; however, hepatic abnormalities are known to occur in this disease[19] and the known relationship between the B vitamins and prevention of fatty infiltration of the liver suggests that B vitamins should be supplied as an oral supplement. A crude preparation which is offered in two to three times the normal maintenance amounts is probably sufficient for this purpose.

The therapeutic regimen described simplifies the care of the patient with fibrosis of the pancreas. It permits parents to think of them as more normal individuals, and allows the children to lead more normal lives. Whether this regimen in any way improves the prognosis of such patients is not known, but on the basis of such evidence as is available it does not seem to have a deleterious effect on the disease. Its major virtue is its simplicity.

Whether the disease will eventually be curable or whether afflicted patients may eventually reach maturity is not known, but one can certainly adopt a hopeful attitude in handling infants and children suffering from fibrosis of the pancreas.

REFERENCES

1. Lowe, C. U., May, C. D. and Reed, S. C.: Fibrosis of the pancreas in infants and children; a statistical study of clinical and hereditary features. Am. J. Dis. Child. 78:349-374, 1949.
2. Neuhauser, E. B. D.: Roentgen changes associated with pancreatic insufficiency in early life. Radiology 46:319-328, 1946.
3. Farber, Sidney: The relation of pancreatic achylia to meconium ileus. J. Pediat. 24:387-392, 1944.
4. Johnstone, D. E.: Studies on the gelatin-liquefying properties of certain bacteria with particular reference to the laboratory diagnosis of cystic fibrosis of the pancreas. Pediatrics 6:351-356, 1950.
5. ———: Studies on cystic fibrosis of the pancreas; role of various diluents and the dilution factor in the interpretation of the x-ray film test for fecal trypsin. Am. J. Dis. Child. 84:191-198, 1952.
6. Shwachman, H.: Progress in the study of "mucoviscidosis." Pediatrics 7:153-163, 1951.
7. Baggenstoss, A. H., Power, M. H. and Grindlay, J. H.: Further studies on the pathogenesis of fibrocystic disease of the pancreas. Arch. Path. 51:510-517, 1951.
8. May, C. D. and McCreary, J. F.: The absorption of vitamin A in celiac disease. J. Pediat. 18:200-209, 1941.
9. West, C. D., Wilson, J. L. and Eyles, R.: Blood amino nitrogen levels; changes in blood amino nitrogen levels following ingestion of proteins and of a protein hydrolysate in infants with normal and with deficient pancreatic function. Am. J. Dis. Child. 72:251-273, 1946.
10. Shohl, A. T., May, C. D. and Shwachman, H.: Studies of nitrogen and fat metabolism in infants and children with pancreatic fibrosis. J. Pediat. 23:267-279, 1943.
11. Shohl, A. T.: Further studies of nitrogen and fat metabolism in infants and children with fibrosis of the pancreas. J. Pediat. 32:180-183, 1948.
12. Hiatt, R. B. and Wilson, P. E.: Celiac syndrome; therapy of meconium ileus. Surg., Gynec. & Obst. 87:317-327, 1948.
13. May, C. D. and Lowe, C. U.: The treatment of fibrosis of the pancreas in infants and children. Pediatrics 1:159-173, 1948.
14. Lowe, C. U. and May, C. D.: Absorption of orally administered emulsified lipid in pancreatic insufficiency in infants and children. In: Oral Fat Emulsions. New York, New York Academy of Sciences (in press).
15. Bruyn, H. B.: Personal communication to the author.
16. May, C. D. and Lowe, C. U.: Fibrosis of the pancreas in infants and children. J. Pediat. 34:663-687, 1949.
17. Wollaeger, E. E., Comfort, M. W., Clagett, O. T. and Osterberg, A. E.: Efficiency of gastrointestinal tract after resection. J.A.M.A. 137:838-848, 1948.
18. May, C. D. and Lowe, C. U.: The absorption of orally administered emulsified lipid in normal children and in children with steatorrhea. J. Clin. Investigation 27:226-230, 1948.
19. Farber, Sidney: Pancreatic function and disease in early life; pathologic changes associated with pancreatic insufficiency in early life. Arch. Path. 37:238-250, 1944.

MEETINGS AND POSTGRADUATE COURSES

University of Kansas Medical Center, Kansas City: Eighth annual course in surgery, January 19-23.

Postgraduate course in pediatrics, January 26-28. Both these courses are sponsored by the University of Kansas in cooperation with the Kansas Medical Society and the Kansas State Board of Health. Send all communications to Extension Program in Medicine, University of Kansas Medical Center, Kansas City 12, Kansas.

Pan American Medical Association: Eighth International Medical Cruise Congress will sail from New York on the S.S. *Nieuw Amsterdam* of the Holland-America line on January 7, 1953, returning to New York January 19. Scientific sessions held each morning while the ship is at sea. Port-Au-Prince, Cartagena, Panama Canal and Havana will be visited.

Editorials

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MEDICAL OBLIGATIONS AND OPPORTUNITIES OF PAN AMERICA

It is very appropriate to report in this journal and at this time of year the visits of Anglo-Americans to our medical neighbors in South America to attend congresses and to visit old and new friends during the past summer and early fall. Twenty years ago there was little or none of this. Latin Americans and Anglo-Americans were essentially strangers to each other and our countries were far from friendly. This was due to a variety of reasons. In the first place the bonds of cultural and scientific interests of Latin America to the Old World were still strong before the holocaust of the second world war. Secondly, there were few connections except those of business and politics and these were not infrequently unfortunate and likely to lead to unfriendly relations. And thirdly, we ourselves in the U.S.A. were only just emerging from a slow process of cultural and scientific development prior to a worldwide recognition of achievement. At about the time of the decline of European leadership under the stress of World War II and its aftermath, we in the U.S.A. had come of age. Our adolescence in the main was over and we had come to stand on our own feet. This was true in various walks of life, including medicine.

The interchange of visits now going on in the profession of medicine between Latin- and Anglo-America bodes well for the future. We are all recognizing our responsibilities as well as our opportunities in the New World to help the Old World which has been less fortunate. We have also a debt of inheritance to pay. Happily we are in a position to do this but to make this mission of ours more successful we must all work together. We must merge the good points of the old French and German and English "schools" with those of the various schools over here—those of the U.S.A., Canada, Mexico, Cuba, and all of South and Central America. Thus we shall have one strong American and, eventually, World "School of Medicine."

The bygone days of rare medical contacts between Latin- and Anglo-American doctors smacked sometimes of commercialism and even exploitation and, although this may still continue here and there in minor degree as it does in our own country, unhappily its memory still lingers in the minds of a few of our own medical and surgical leaders causing them to hesitate to accept, as I am sure they should, the role of cooperative medical endeavor throughout all the Americas. This year especially, many of our ablest physicians and surgeons did attend and take part in the Congresses of Cardiology and Hematology in Buenos Aires and of Chest Diseases in Rio de Janeiro. En route to and from these congresses nearly all of those of us who attended also visited other medical centers in both the East and the West of the continent. We learned, I am sure, as much as we taught, and everywhere found the warmest evidences of

hospitality and true friendship. The result will doubtless be more medical visitors to our own clinics and laboratories and a strengthening of friendly ties, not only medically but politically as well, between Latin- and Anglo-America. The medical profession is in a strong position, perhaps stronger than any other, to dedicate itself to the furtherance of peace and happiness as well as of health throughout the whole world.

PAUL D. WHITE

THE STUDY OF PAIN

ONE of the unachieved goals of pharmacologic research is a technic of measuring accurately the sensation of pain. A variety of technics have been offered for the purpose but thus far the problem is not solved. In a recent report of research in this field by Dr. Henry K. Beecher[1] of the Anesthesia Laboratory of Harvard Medical School, he says:

> For the present at least the question of whether one can measure intensity of pain or the intensity of any of the types of subjective responses mentioned must be left open.

Nevertheless progress is being made in research; some 17 studies have been completed under Dr. Beecher's direction. These studies have been supported by the Medical Research and Development Board of the U.S. Army, by the U.S. Public Health Service and by the Committee on Narcotics and Drug Addiction of the National Research Council. The latter researches were largely supported with funds contributed by a group of interested pharmaceutical manufacturers who obviously have a great stake in the solution of this problem.

Among the subjective conditions to be studied are included the mental state, attention, learning, association, memory, critical judgment and sensory phenomena. Certainly the psychiatrists are as much interested as are the pharmacologists, the physicians and the manufacturers of drugs in progress of research in these fields. The drugs chiefly concerned are those that depress the central nervous system and man is of necessity the essential animal for investigation. At present analgesic agents are commonly screened in lower animals and the tests depend on reflexes and the extent to which the drug will depress various reflexes. Nevertheless the relationship between pain-relieving power and depression of reflexes is not clear.

Dr. Beecher has made controlled studies of the Harvey-Wolff-Goodell technic which involves projecting a measured amount of heat on the skin until pain is produced but his results fail to confirm the value of this method. His group concludes that it is useless to look with this method for subtleties in pain-relieving power such as might distinguish one narcotic from another.

As an indication of the difference between using the conscious human being in tests of pain with other experimental pain methods, Dr. Beecher says, "Anyone who has had his tonsils out and who has had to chew 5 gr. of aspirin before he could swallow his food knows that aspirin does have local analgesic power. The man with a headache, with a toothache, with the pain of arthritis, with wound pain, does not need a learned treatise to tell him that aspirin is indeed an analgesic agent, and a fairly good one; yet these experimental pain methods usually failed to reveal what we all know." A technic was developed by the Beecher group which can differentiate satisfactorily between aspirin and a placebo or aspirin and morphine.

The Harvard investigators are convinced that the use of pain of experimental origin in man is artificial and that one must depend on natural pain for conclusive study. This belief is based on the observation that emotion can block pain, that extrinsic factors and lack of attention to wounds as in games or during fighting can block pain and that a disregard for wounds is often associated with blocking of pain. A great difference exists between pain produced in the laboratory and pain of the patient in the sick bed. As controls comparisons were made between capsules containing placebos and capsules containing analgesics of the narcotic class (for instance, morphine in a standard dose and new agents), all of the capsules being of identical appearance. A technic of thorough randomization

was found to be essential with the order of the agents used varying from time to time. Incidentally some people were found who are designated as "placebo reactors" because they react favorably to placebos far beyond the reactions of other individuals. These people are not malingerers or neurotics but allowance must be made for a certain percentage of such persons in every group of people tested.

The ultimate value of the studies already made by Dr. Beecher's group and those prospected for the future is so tremendous as to be incalculable. The methods may seem tedious and costly but the group insists that they are not more costly than the empiric method and that they will, in the long run, be much less so. They are far superior to the old-fashioned method of simply distributing drugs to practically everybody and then by trial and error arriving at an exact evaluation. Again to quote Dr. Beecher: "After all the centuries morphine or opium has been used, common sense in this country has arrived at a dose that is twice as large (15 mg.) as the one that gives essentially the maximum pain relief (8 mg.)."

Much of the most important research in medical science has come from the development of important new technics. The technics now in process of development by the Beecher group should yield rich rewards in the years to come.

MORRIS FISHBEIN

1. Beecher, Henry K.: Experimental pharmacology and measurement of the subjective response. Science 116:157-162 (August 15) 1952.

THE HISTORY OF PUERPERAL SEPSIS

In 1845 Ignaz Philipp Semmelweis became professor of obstetrics at Budapest and in 1861 he published the book in which he championed asepsis in obstetrics. Toward the end of the previous century the infectious nature of puerperal fever was becoming recognized through the work of Smellie, William Hunter and particularly Charles White of Manchester. The last-named had urged cleanliness in the environment of delivery and segregation of febrile patients. In 1842 Oliver Wendell Holmes published his famous article, "On the contagiousness of puerperal fever." Semmelweis insisted that hands be washed carefully and that rooms be disinfected with calcium chloride. Twenty years had to pass before his doctrine was generally accepted.

Recently Dr. Anne Elizabeth Caldwell of the United States Army Medical Department has called attention to some additional early observations on puerperal fever that merit consideration. In the *London Medical Gazette*, February 18, 1842, appeared a lecture by Thomas Watson who said that the infection of puerperal sepsis can be, and frequently is, carried from one patient to another by the hands of the accoucheur, and that this can be prevented by disinfecting the hands with a chlorine solution. He recognized the possibility of contamination from within. Moreover he said:

> Indeed I believe that these cases of puerperal fever occurring in succession to the same practitioner, are examples of something more than ordinary contagion, operating through the medium of a tainted atmosphere. I believe them to be instances of direct inoculation.

Dr. Thomas Watson actually anticipated another great discovery for prevention of sepsis since he wrote:

> In these days of ready invention, a glove, I think, might be devised, which should be impervious to fluid and yet so thin and pliant as not to interfere materially with the delicate sense of touch required in these manipulations. One such glove, if such shall ever be fabricated and adopted, might well be sacrificed to the safety of the mother in every labor.

Incidentally, Dr. Caldwell points out, Charles Goodyear developed the process of vulcanization of rubber in 1839 and obtained a patent on it in 1844.

Two months after Watson's lecture, Robert Storrs published the report of an outbreak of puerperal sepsis in Doncaster in which he asserted that the infection was "propagated from one individual to another." Oliver Wen-

dell Holmes mentions in his essay both Storr's paper and the lecture by Watson.

Most medical discovery is not the product of one mind but rather the product of a period in which many observations are made and concepts are discussed and gradually focused toward a logical result.

MORRIS FISHBEIN

IRON AND IRON COMPOUNDS IN ANEMIA

In his new textbook[1] of pharmacology Professor William T. Salter, professor of pharmacology in Yale University School of Medicine, recalls the ancient story of the Greek who sought the shrine of Aesculapius for the treatment of impotence. In his impious youth the man had plunged a dagger into a tree in a sacred grove. Returning to the forest, he removed the rusty dagger from the tree and soaked it in wine which he ultimately drank. Apparently he received in this way enough iron to relieve his anemia and thereby he was also cured of his impotence.

From the time of the ancient Greeks until the recognition of the value of iron, of liver extracts, folic acid and vitamin B_{12} for the control of various forms of anemia, the metallic substance has had the interest of the medical profession. The forms chiefly used have been the ferrous iron and the ferric iron. The importance of iron is especially great because of its part in the formation of hemoglobin which serves as a reservoir of oxygen for the tissues. Iron is constantly being freed from the hemoglobin and is then salvaged by the blood so that an adult male may retain health on an essentially iron-free diet. The minimum amount required daily is about 5.0 mg. and the average American diet contains about 16 mg. a day because of the vegetables and the meats with their iron content. Menstruating women need at least 16 mg. daily and pregnant women over 20 mg. daily to maintain the iron in the blood. A lack of iron is associated with hypochromic anemia and undersized red cells. Such anemias are usually caused by chronic blood loss, rapid growth and similar conditions. Studies have shown that the absorption of iron is about 8 per cent of the amount given but the gastrointestinal tract may absorb a greater percentage of iron when there is a special need for it. Because of the limited absorption, it is customary to give a large excess of iron. Professor Salter says that "in the case of infants who cannot swallow tablets, it is common practice to give the elixir of ferrous sulfate containing about 0.1 gm. of the medication three times a day. Ferrous sulfate, if given in excess, will irritate the gastrointestinal tract and produce alternately constipation and diarrhea."

There are many other preparations of iron besides the ferrous sulfate. Investigations have shown, however, that organic iron is probably converted into inorganic ferrous iron before being absorbed. Apparently other preparations are not better absorbed than ferrous sulfate or ferrous gluconate. Recently several publications have appeared warning against the dangers of tablets of ferrous sulfate for children.[2] Some who have eaten ferrous sulfate tablets developed bloody vomiting, shock, coma, hypotonia and tarry diarrhea, *The British Medical Journal* warned editorially. Recently 3 cases of ferrous sulfate poisoning were described in the *Journal of Pediatrics*.[3] Obviously iron follows the principle of practically all other remedies in the pharmacopeia: Used under proper conditions in proper dosage, it is beneficial; used wrongly or in improper dosage, it may be harmful. The intravenous use of iron is not well established. In some instances hemosiderosis has occurred. Perhaps in the case of women during pregnancy and lactation, intravenous iron may be warranted to avoid serious gastrointestinal symptoms.

MORRIS FISHBEIN

1. Salter, William T.: A Textbook of Pharmacology. Philadelphia, W. B. Saunders Company, 1952, p. 412.
2. Editorial. Canad. M. A. J. 66:278 (March) 1952.
3. Duffy, Thomas L. and Diehl, A. M.: J. Pediat. 40:1 (January) 1952.
4. Heck, F. J.: Proper medication for the anemias. J.A.M.A. 148:783, 1952.

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THE MEDICAL Bookman

► THE 1951 YEAR BOOK OF ENDOCRINOLOGY

Edited by Gilbert S. Gordan, M.D., Assistant Professor of Medicine, University of California School of Medicine, San Francisco. 415 pages, illustrated. 1952, The Year Book Publishers, Inc., Chicago. $5.00.

The ever widening scope of hormone therapy is stressed in the current endocrinology Year Book. Nearly one-fifth of the text is devoted to cortisone and allied substances while a separate chapter deals with use of sex hormones in the treatment of neoplastic diseases and yet another section is concerned with the general anabolic activity of the androgens. The usual endocrine disorders are well covered, especially the recent measures for treating hyperthyroidism. Metabolic bone disorders, calcium metabolism, diabetes mellitus and carbohydrate metabolism are given attention and several articles on the use of NPH insulin are abstracted. As in previous editions, there are abstracts and discussions of the best work in the field published during the year. This edition should be especially attractive to all physicians since so many advances in the clinical use of hormones for non-endocrine disorders have been made recently.

T. B. G.

► NORMAL BLOOD PRESSURE AND HYPERTENSION

By Arthur M. Master, M.D., Charles I. Garfield, M.D. and Max B. Walters, M.D., The Mount Sinai Hospital, New York City. 144 pages with 36 illustrations. 1952, Lea & Febiger, Philadelphia. $4.00.

To establish the true limits of normal blood pressure, the work upon which this book is based was undertaken. The blood pressure of 74,000 men and women between the ages of 15 and 65 years was determined. The results of this large scale sampling were analyzed statistically and are lucidly presented in the text. The mean blood pressure and the normal range are given with regard to age, height, weight and sex. A useful removable table showing the new normal range and limits of blood pressure is included.

In addition, the interpretation and application of the new criteria for hypertension recommended are discussed, the authors' object being to lessen the frequency with which the diagnosis of hypertensive vascular disease is made erroneously.

The book also offers an interesting history of sphygmomanometry and traces the development of the modern sphygmomanometer. A separate chapter deals with factors which affect the blood pressure and is most helpful in evaluating blood pressure readings obtained on patients.

T. B. G.

► ESSENTIALS OF DERMATOLOGY

By Norman Tobias, M.D., Associate Clinical Professor of Dermatology, St. Louis University. Ed. 4. 596 pages with 186 figures and 3 color plates. 1952, J. B. Lippincott Company, Philadelphia. $6.00.

Following a basic survey of the subject is a careful classification of the many skin diseases.

In spite of its size, coverage of material in this text is sketchy. More space could be devoted to the more common dermatoses and the many rare dermatoses completely deleted. By attempting to cover the entire field, the author sacrifices information to cataloging. To its credit one must say that the book is well illustrated and is of value as a handbook for rapid reference.

I. F.

(Continued on page A-50)

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► THE METABOLIC RESPONSE TO SURGERY

By Francis D. Moore, M.D., Moseley Professor of Surgery, Harvard Medical School, and Margaret R. Ball, A.B., Department of Surgery, Harvard Medical School, Boston, Massachusetts. 167 pages with 56 illustrations. 1952, Charles C Thomas, Springfield, Illinois. $7.50.

Another in the American Lecture Series, this is a progress report of the research studies carried out at the Harvard Medical School in the problem of metabolism in the surgical patient. The whole problem of the effects of surgery on the patient is broken down into various components and analyzed in an objective way, eliminating largely empiric methods based on impressions only.

An interesting method of describing the extent of trauma is presented: A loose scale of 10 was adopted as a semiquantitative framework for interpretation of the response. On this scale a third degree burn of 25 per cent or more of the body surface is placed at the top of the scale. Multiple wounds including major or compound fractures and penetrating wounds of the chest and abdomen are placed on scale 9, 8 or 7. Extensive multivisceral operation is also placed on scale 9, 8 or 7. Scale 5 is best represented by ordinary major anastomotic gastrointestinal surgery. Cholecystectomy, appendectomy and thyroidectomy in their simplest forms are placed on scale 3 and minor surgical procedures on scale 1.

Some findings of the study are that the transient loss of nitrogen following injury is a normal response and is correlated with good recovery. Depleted patients lose less nitrogen than normal patients and in general have a less satisfactory convalescence. A patient cannot recover, regain strength and return to work unless there is a return to positive nitrogen balance. The authors feel that the greatest need at present is for a wider use of the 24 hour urine-nitrogen determination. Stress is placed on the need for thinking in terms of balance in regard to elements gained and utilized in daily diet and metabolism, particularly with nitrogen, protein, sodium, chloride and caloric energy. The authors believe that the dangerously ill patient today is not a problem in diagnosis, sepsis, technic or pain but is a problem in endocrine balance, in nutritional disturbance and in extrarenal losses.

Y. S.

► APPLIED PHYSIOLOGY

By Samson Wright, M.D., John Astor Professor of Physiology, University of London, Middlesex Hospital Medical School. With the collaboration of Montague Maizels, M.D. Ed. 9. 1,190 pages, illustrated. 1952, Oxford University Press, New York. $9.00.

A new edition of this best seller in medical literature will be welcomed by clinicians, clinical pathologists and medical students. Dr. Wright has enlisted as collaborators a professor of clinical pathology, Dr. Montague Maizels, and a biochemist, Dr. John B. Jepson. These authors have virtually prepared a new book. More than half the text of the last edition has been rewritten and the subject matter has been rearranged. The present volume contains nearly three times as many pages as the first edition. If any criticism is to be made of this classic in its present form, it is that it is getting too large and is awkward to hold. However, it is packed full of interesting material. The references are numerous and are carried as footnote references on each page. They would be found more readily if alphabetically arranged at the end of each chapter. Of course, this is merely a matter of opinion.

An entirely new feature of this ninth, or new, edition is the opening section on the regulation of the constancy of the internal environment (milieu interne). The first 132 pages are devoted to this subject. There are in all now 11 divisions. In addition to the first division, the subjects presented are on the heart, blood and circulation, respiration, nervous system, autonomic nervous system, digestion, metabolism, endocrine control of metabolism, nutrition and reproduction.

There are 688 illustrations; the eighth edition had 515, while the first edition published in 1926 had only 37. The author states that from his experience illustrations may not be adequately or properly used. While many of the illustrations have been redrawn the source is always given. Wright states: "Any paper that contains a figure worth borrowing is invariably worth

(Continued on page A-52)

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reading." The "Glossary of Anatomical Nomenclature" compared to the old terminology presented in all editions beginning with the second has been dropped from this edition as no longer necessary.

Mention must be made of the mottos that have been found on the page facing the preface since the fifth edition. The first wise saying found there was "The simple believeth every word, but the prudent man looketh well to his going" (Proverbs 14:15). This same motto was used also in the seventh edition, with an additional quotation from the student number of the *Lancet*, August 1939; namely, "The student must continue to read good English and especially poetry, not only because use of words is vital to the doctor, but also that he may retain the flavour of a lovely language while he is studying from his textbooks." The quotations used in the eighth edition were too long, and in this, the ninth edition, a delightful epigram has been used which will warm the heart of every true teacher. "Rabbi Akiba (in Roman captivity) to his favourite pupil Simeon Yochai: 'My son, more than the calf wishes to suck does the cow yearn to suckle.' "

A. H. S.

► THE AUTONOMIC NERVOUS SYSTEM

By James C. White, M.D., Associate Professor of Surgery, Harvard Medical School; Reginald H. Smithwick, M.D., Professor and Chairman of the Department of Surgery, Boston University School of Medicine, and Fiorindo A. Simeone, M.D., formerly Assistant Professor of Surgery, Harvard Medical School, Boston. Ed. 3. 552 pages with 70 illustrations. 1952, The Macmillan Company, New York. $12.00.

In this third edition of their book, the authors have gathered the most recent knowledge regarding the structure and function of the autonomic nervous system and have included their own experience as well as that of others regarding the methods whereby surgery can be applied in the various disorders of this system.

Although the authors claim that this book is devoted to the surgical aspects of this system, the monograph is far more comprehensive. The book actually is divided into three parts with only the third section dealing with surgical technics. The first section consists of a well illustrated, concise discussion of the anatomy, pharmacology and physiology of the autonomic nervous system. In this section the authors have succeeded in reviewing a vast literature and present this complicated material in a readable and useful manner. The second portion of the text comprises a critical and unbiased review of the role of sympathectomy in modifying abnormal activity on the part of smooth muscle, faulty visceral function and pain. This section will prove of value to anyone in the practice of medicine who must decide the value of sympathectomy in any particular case. So comprehensive is this review that it covers the entire range of medical practice and practically every medical specialty.

This book is one of the most useful and practical that has appeared on the subject of the autonomic nervous system. It is highly recommended not only to the doctor in general practice but also to the entire profession.

A. B. B.

► THE CLINICAL USE OF FLUID AND ELECTROLYTE

By John H. Bland, M.D., Assistant Professor of Medicine, University of Vermont College of Medicine. 259 pages with 75 figures. 1952, W. B. Saunders Company, Philadelphia & London. $6.50.

Correlation of established facts concerning electrolyte and fluid physiology with their practical application in medical and surgical problems is the accomplished purpose of this book. Much has been learned about the normal chemical anatomy of the body and about the alterations due to various illnesses. However, it appears characteristic of this facet of medicine that a regrettable delay separates laboratory acquisition of information and its general use at the bedside. Many physicians most adept at diagnosis and treatment of disease find themselves dissatisfied with their ability to cope with electrolyte disorders.

A stumbling block to many are the terms employed. Osmola, equivalents, molecular weights and valence tend to be foreboding and to discourage study in the field. Dr. Bland wisely begins his presentation with a clear discussion of the terms so necessary for proper understanding

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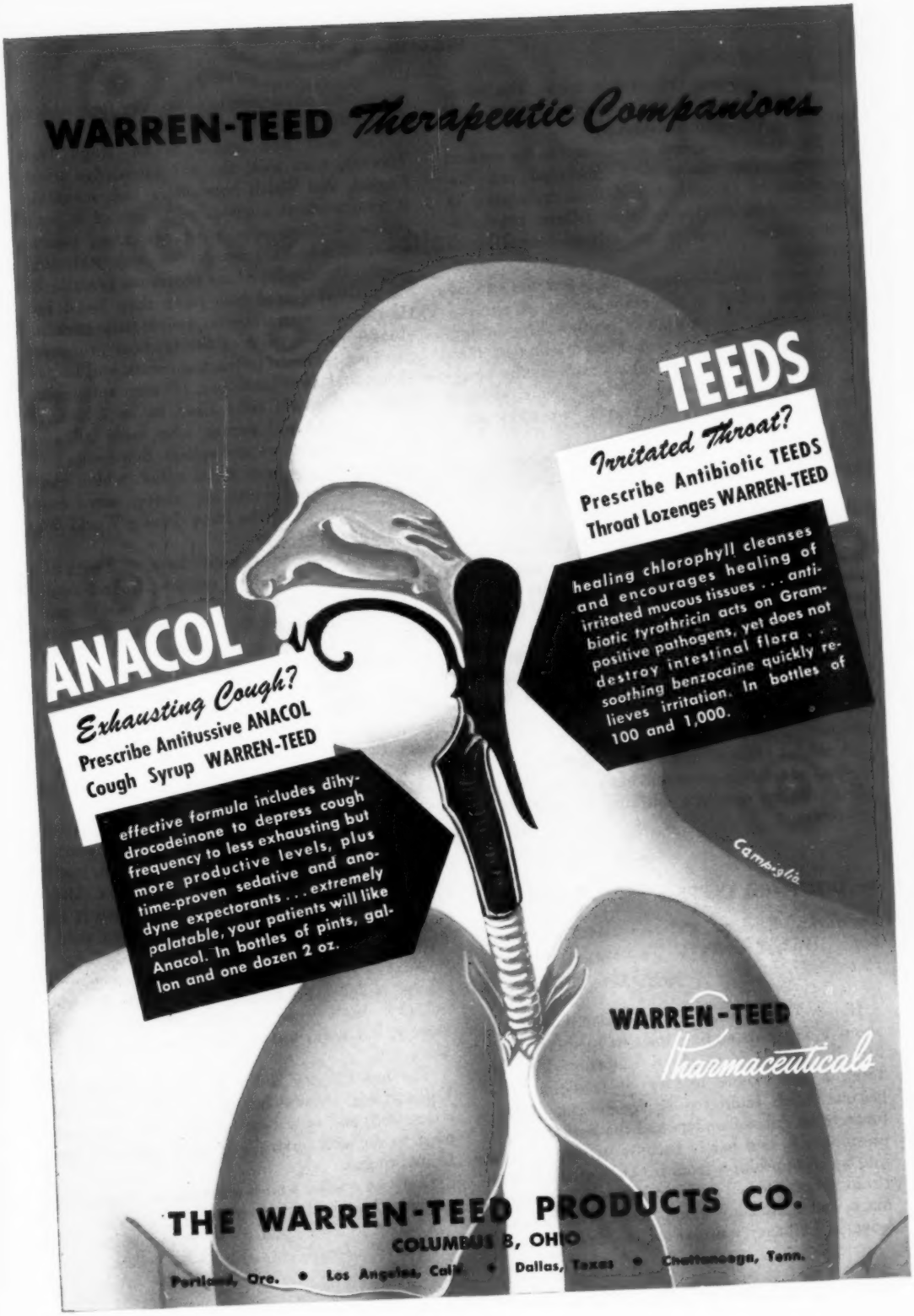

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and presentation of electrolyte status. The initial chapter then proceeds to a lucid presentation of the normal chemical anatomy.

Subsequent chapters are devoted to the various abnormalities encountered. Included are discussions of electrolyte and fluid imbalance in dehydration, congestive heart failure, renal disease, diabetes mellitus and adrenocortical insufficiency.

A most valuable chapter considers the special problems found in the management of electrolyte imbalance in geriatric patients. The author has had extensive personal experience in this field. He feels that too often death in the aged is wrongly attributed to "old age" when an unrecognized or improperly treated electrolyte disorder is, in fact, to blame.

Fluid management in surgical and pediatric patients also receives separate and detailed attention. In these sections, as in others, various laboratory tests most likely to be helpful are recommended. Replacement therapy is discussed with the objective of instructing the reader to choose the proper type of repair solution as well as to determine the amount of water and electrolytes to be administered.

Other features receiving special attention are potassium metabolism, environmental heat, other physical stresses, such as burns, and the influence of ACTH and cortisone on the chemical makeup of the body.

A useful table of the sodium and potassium content of foods is given and each chapter is supplied with an excellent selection of appropriate references.

T. B. G.

► DOCTORS DIFFER

By Harley Williams. 253 pages with 8 illustrations. 1952, Charles C Thomas, Springfield, Illinois. $5.50.

Harley Williams has written a delightful book about a few outstanding men in medicine. His first big article is on John Elliotson, 1791 to 1868, a remarkable teacher of medicine who became much interested in hypnotism. Unfortunately he did not understand the nature of the phenomenon, and partly because of this, he ran into much opposition from his colleagues. James Braid, who followed him, understood hypnotism much better, and got along better with his colleagues. Elliotson was one of the first of many prominent physicians to constantly feud with the Board of Governors of his hospital!

The next fine article is on Hugh Owen Thomas, who took the old knowledge of the English and Welsh bonesetters and, combining it with modern science, made out of it orthopedics. Thomas was a strange man, possibly schizoid, who did not get on well with other people. He developed an enormous practice but his patients feared him more than loved him. He was an eccentric who deliberately remained obscure and outside of the medical profession. He never bothered to teach students, and he gave no hospital demonstrations. He even antagonized those who would have liked to help him. He was a mechanical genius who made all sorts of useful appliances and splints. Some men have said that his favorite metal splint, which could quickly be twisted into any shape, saved more lives of soldiers at the front during World War I than any medicine.

Thomas' knowledge would have died with him if it hadn't been for his nephew, Robert Jones. Fortunately Robert Jones was a most lovable man, very different from his uncle. When the uncle died he took over the enormous practice. He was the first to use the x-rays in orthopedics. He taught students, and worked 14 hours a day in his clinic. On Sundays he had a free clinic in which he saw several thousand patients a year. Building wisely on the foundations of his uncle, Robert Jones made orthopedics into a splendid specialty.

The next chapter describes the mental development of James Mackenzie, a general practitioner who, working hard in a small town, made himself the world's leading heart specialist. After success came to him in London, he gave it all up and went back to a small town to study symptoms.

Next is a chapter on William Macewen and Victor Horsley, the two great founders of brain surgery. Both were unusual men of driving energy, but unfortunately they were not easy to work with.

The last chapter is on Robert W. Philip of England who showed how tuberculosis could be conquered, and on Edward L. Trudeau who had most to do with controlling tuberculosis in the United States.

Every physician who loves medical biography will greatly enjoy this book.

W. C. A.

(Continued on page A-56)

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Books received will be acknowledged in this department each month. As space permits, books of principal interest to our readers will be reviewed more extensively.

Manual of Gynecology. By E. Stewart Taylor, M.D., Head of the Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Denver. 204 pages with 70 illustrations. 1952, Lea & Febiger, Philadelphia. $4.50.

Progress in Fundamental Medicine. Edited by J. F. A. McManus, M.D., University of Virginia. Contributors: Paul Cannon, J. A. Cunningham, Paul Klemperer, Albert Kligman, G. K. Mallory, Tracy B. Mallory, J. C. Paterson, L. B. Stoddard, W. Kenneth Cuyler and J. P. Wyatt. 316 pages with 74 illustrations and 2 color plates. 1952, Lea & Febiger, Philadelphia. $9.00.

1952 Year Book of Medicine. Edited by Paul B. Beeson, M.D., J. Burns Amberson, M.D., William B. Castle, M.D., Tinsley R. Harrison, M.D., George B. Eusterman, M.D. and Robert H. Williams, M.D. 735 pages, illustrated. 1952, The Year Book Publishers, Inc., Chicago. $6.00.

Multiple Sclerosis; Application of Rehabilitation Techniques. By Edward E. Gordon, M.D., Director of the Institute for the Crippled and Disabled, New York City. 54 pages with 54 figures. Available without cost to physicians. Address National Multiple Sclerosis Society, 270 Park Avenue, New York 17, New York. Four additional pamphlets are also available which will be sent to physicians on request for distribution to their patients. Titles are: (1) A Home Program for Independently Ambulatory Patients; (2) A Home Program for Patients Ambulatory with Aids; (3) A Home Program for Wheel Chair Patients, and (4) A Home Program for the Care of Bed Patients.

Correlative Neuroanatomy and Functional Neurology. By Joseph J. McDonald, M.D., Professor of Surgery, Columbia University, New York. Ed. 6. 263 pages, illustrated. 1952, Lange Medical Publications, Los Altos, California. $4.00.

Neurosurgery in General Practice. By Adrien ver Brugghen, M.B., Clinical Professor of Neurological Surgery (Rush), University of Illinois College of Medicine, Chicago. 665 pages with 282 figures. 1952, Charles C Thomas, Springfield, Illinois. $14.00.

An Introduction to Medical Science. By William Boyd, Professor of Pathology, University of British Columbia, Vancouver, B. C. Ed. 4. 304 pages with 124 illustrations and 3 color plates. 1952, Lea & Febiger, Philadelphia. $4.50.

Synopsis of Pathology. By W. A. D. Anderson, M.D., Professor of Pathology, Marquette University School of Medicine, Milwaukee. Ed. 3. 788 pages with 344 illustrations and 13 color plates. 1952, The C. V. Mosby Company, St. Louis. $8.00.

The History of American Epidemiology. By C.-E. A. Winslow, Dr. P.H., Wilson G. Smillie, M.D., James A. Doull, M.D. and John E. Gordon, M.D. Edited by Franklin H. Top, M.D., Professor of Epidemiology and Pediatrics, University of Minnesota College of Medical Sciences, Minneapolis. 190 pages. 1952, The C. V. Mosby Company, St. Louis. $4.75.

Acute Peripheral Arterial Occlusion. By William D. Holden, M.D., Western Reserve University School of Medicine, Cleveland. 66 pages. 1952, Charles C Thomas, Springfield, Illinois. $2.35.

The Moral Theory of Behavior; A New Answer to the Enigma of Mental Illness. By Frank R. Barta, M.D., Director, Department of Psychiatry and Neurology, Creighton University School of Medicine, Omaha, Nebraska. 35 pages. 1952, Charles C Thomas, Springfield, Illinois. $2.00.

Post-Operative Care. By H. J. B. Atkins, D.M., M.CH., F.R.C.S., Surgeon and Director of the Department of Surgery, Guy's Hospital, London. Ed. 4. 338 pages, illustrated. 1952, Charles C Thomas, Springfield, Illinois. $6.75.

Post-Graduate Lectures on Orthopedic Diagnosis and Indications. By Arthur Steindler, M.D., Professor of Orthopedic Surgery, State University of Iowa, Iowa City. Vol. IV: Section A—Arthritis and Diseases of Muscles, Bursae, Tendons and Fasciae; Section B—Deficiency and Degenerative Diseases of the Locomotor System. 312 pages with 276 figures. 1952, Charles C Thomas, Springfield, Illinois. $9.75.

Essentials of Infant Feeding for Physicians. By Herman Frederic Meyer, M.D., Assistant Professor of Pediatrics, Northwestern University School of Medicine, Chicago. 252 pages with 13 illustrations. 1952, Charles C Thomas, Springfield, Illinois. $6.75.

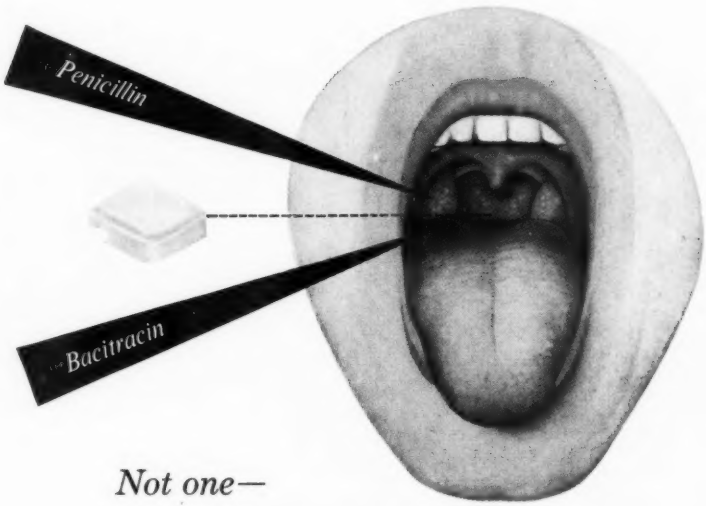
Cornell Conferences on Therapy. Edited by Harry Gold, M.D. Editorial Board: David P. Barr, M.D., McKeen Cattell, M.D., Frank C. Ferguson, Jr., M.D., Frank Glenn, M.D. and George Reader, M.D. Vol. 5. 299 pages. 1952, The Macmillan Company, New York. $4.00.

Radiologic Diagnosis of the Lower Urinary Tract. By Donald E. Beard, M.D., William E. Goodyear, M.D. and H. Stephen Weens, M.D., Emory University School of Medicine, Atlanta, Georgia. 143 pages with 280 figures. 1952, Charles C Thomas, Springfield, Illinois. $6.50.

Sexual Adjustment in Marriage. By Henry Olsen, M.D., Copenhagen, Denmark. 310 pages. 1952, Henry Holt and Company, New York. $6.00.

Pediatrics in General Practice. By James G. Hughes, M.D., Professor of Pediatrics, University of Tennessee College of Medicine, Memphis. 735 pages with 178 figures. 1952, McGraw-Hill Book Company, Inc., New York, Toronto & London. $14.00.

The 1952 Year Book of Obstetrics and Gynecology. Edited by J. P. Greenhill, M.D., Professor of Gynecology, Cook County Graduate School of Medicine, Chicago. 575 pages. 1952, The Year Book Publishers, Inc., Chicago. $5.50.



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1. Eagle, H., and Fleischman, R.: Proc. Soc. Exper. Biol. & Med. *68*:415 (June) 1948.

2. Bachman, M.C.: J. Clin. Invest. *28*:864 (Sept.) 1949.

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